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JULY 1955

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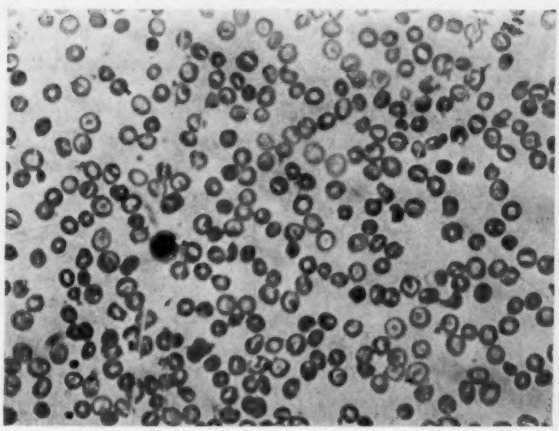

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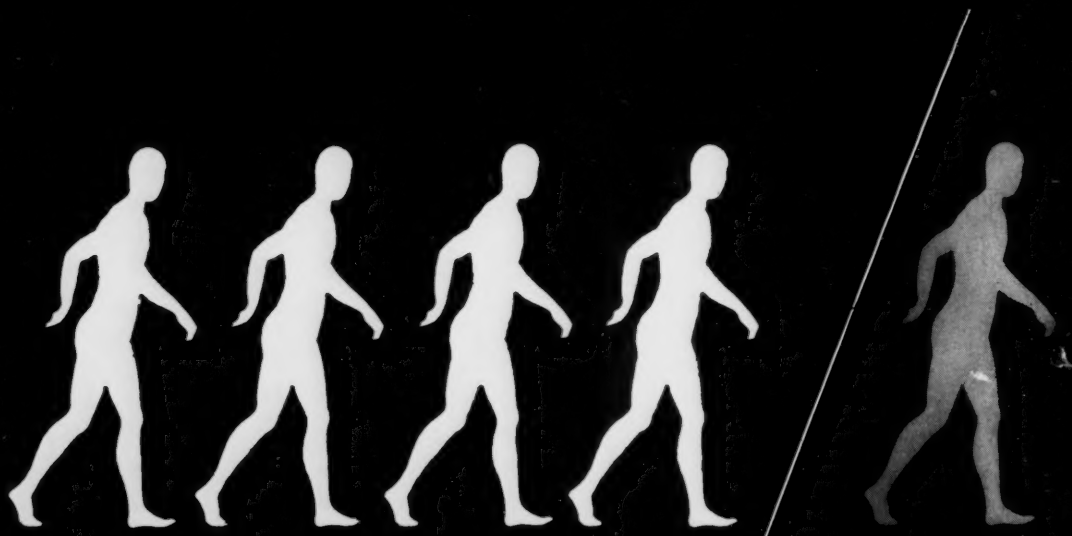

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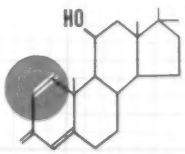

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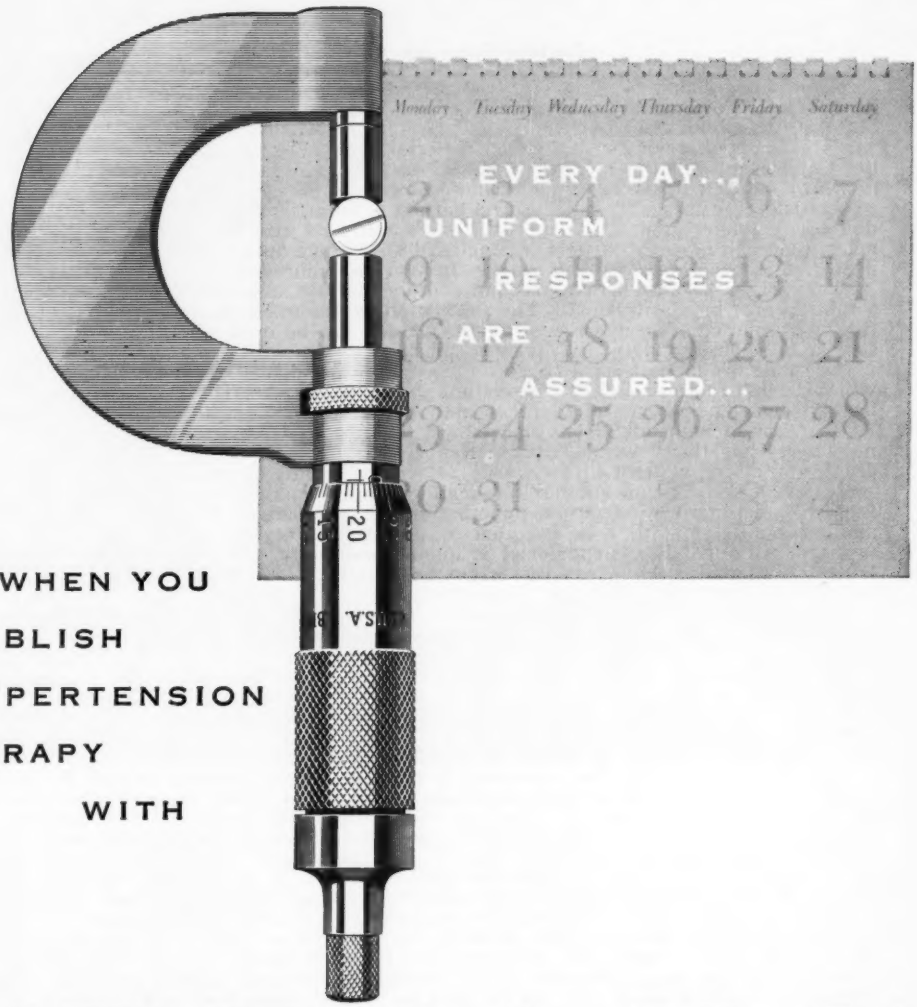

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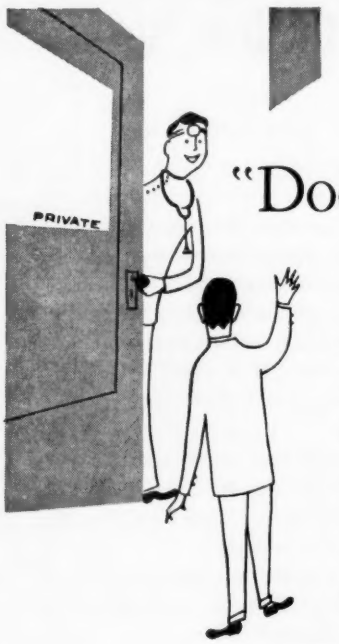

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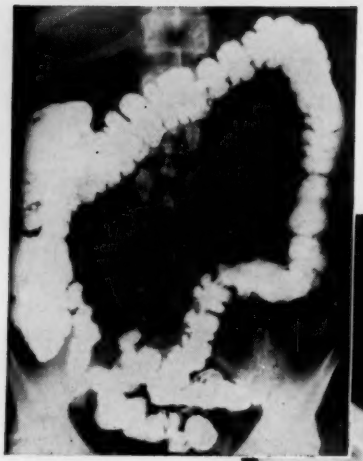

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Types of Death in Acute Myocardial Infarction

NORMAN W. McQUAY, M.D.
JESSE E. EDWARDS, M.D.
and
HOWARD B. BURCHELL, M.D., Rochester, Minn.

When a person dies days or weeks after acute myocardial infarction develops, the exact precipitating cause and mechanism of death often pose enigmas. To know the cause and mechanism of death is not of academic interest alone; such knowledge may prove of value in the more intelligent approach to the treatment of patients with this common disease.

The primary purpose of this study was to determine, in so far as possible, the type of death in a series of patients who died of acute myocardial infarction, with the hope of shedding additional light on the mechanism of death in other patients having this condition.

MATERIALS AND METHODS

A study was made of 133 cases of fatal acute myocardial infarction in which necropsy was performed and in which the age and sex of the patients were known. The acute infarcts of these patients were classified as to their anatomic characteristics and as to whether or not they were associated with healed myocardial infarcts. The clinical and pathologic features were studied in order that the type of death for each patient could be determined.

Submitted for publication May 19, 1955.

Abridgment of thesis submitted by Dr. McQuay to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

Fellow in Medicine, Mayo Foundation (Dr. McQuay); Section of Pathologic Anatomy (Dr. Edwards) and Section of Medicine (Dr. Burchell), Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Selection of Cases

In each of the 133 consecutive cases the following criteria were fulfilled: 1. Death of the patient occurred in hospital in Rochester, Minn., within the five-year period Jan. 1, 1946, to Dec. 31, 1950. 2. Necropsy was performed by the Section of Pathologic Anatomy of the Mayo Clinic. 3. The myocardial infarct was less than four weeks old, as based on the history and the histologic criteria of Mallory, White, and Salcedo-Salgar.[1] 4. The acute infarct in each case measured 2 cm. or more in at least one dimension.

Classification of Myocardial Infarcts

In each case the heart was available for restudy. The hearts were examined to determine the presence or absence of previous myocardial infarction; if an old infarct was present its nature was described as either conglomerate or patchy. The acute infarct was identified both grossly and microscopically and according to the region of the heart in which it was located and to the amount of cardiac muscle involved.

In many of the hearts the ventricles had been cut in a series of five cross sections, Slice 1 being at the apex and Slice 5 at the base. To determine whether other infarcts were present that were more recent than the acute infarct for which the patient was hospitalized, "spot check" sections were taken from three of the five cross sections. Each of the three slices used represented a portion of the heart supplied by one of the coronary arteries (Fig. 1). The sections were taken as follows: 1. For the region supplied by the anterior descending coronary

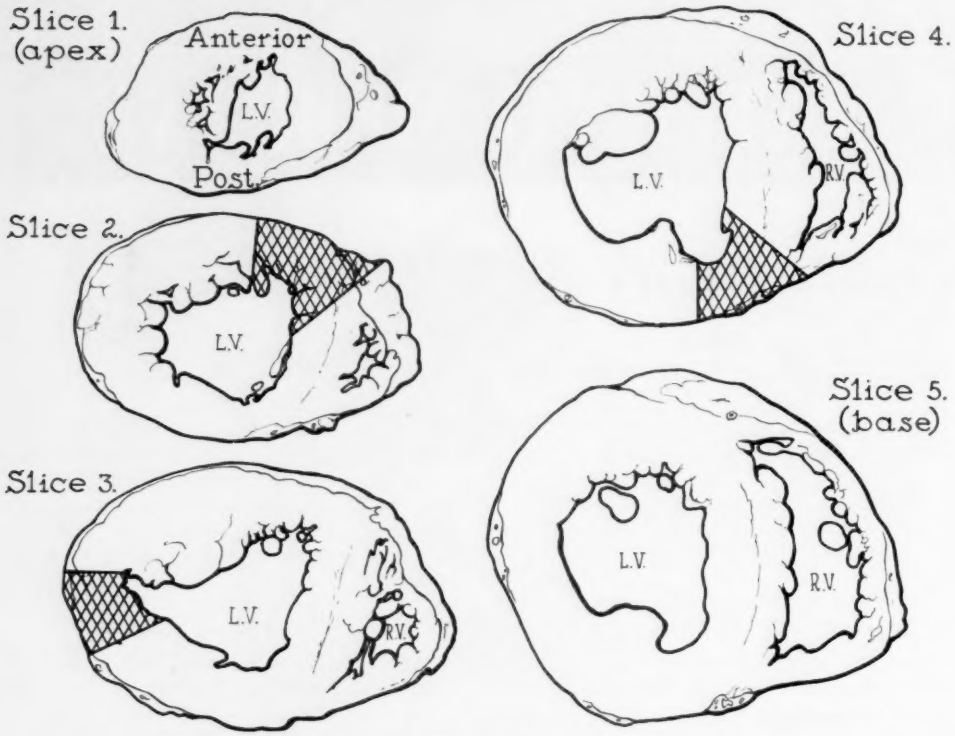

Fig. 1.—Cross sections of the ventricles viewed from the base toward the apex, in which Slice 1 represents the apical region and Slice 5, the basal region. For "spot checking" the three coronary arterial regions, sections were taken from the areas indicated by cross hatching. The region supplied by the anterior descending coronary artery was sampled in the anterior portion of the second slice and adjacent ventricular septum; that for the left circumflex coronary artery was sampled in the lateral region of the third slice, and that for the right coronary artery was taken from the posterior region of the fourth slice and adjacent ventricular septum.

artery a section was taken from Slice 2 which contained anterior wall of the left ventricle and the anterior portion of the ventricular septum. 2. For the region supplied by the left circumflex coronary artery a section was taken from Slice 3 which contained lateral wall of the left ventricle between the anterior and posterior papillary muscles. 3. For the region supplied by the right coronary artery a section was taken from Slice 4 which contained posterior wall of the left ventricle and posterior portion of the ventricular septum. Sections were also made from the portions showing obvious infarction.

The coronary arteries were cross sectioned at 3 mm. intervals along their entire course. Histologic sections were studied to evaluate gross impressions concerning the presence or absence of acute occlusion.

Healed Infarcts.—"Healed infarcts" was the designation given to scars encountered. In some instances the healed infarct was represented by one conglomerate mass of scar tissue. Such healed infarcts, when they measured at least 2 cm. in diameter, were designated as "conglomerate." In other instances healed infarction was represented by a zone of myocardium in which various-sized scars, all smaller than 2 cm. in diameter, alternated with intact muscle. Healed infarcts of this character were termed "patchy." Infarction with lesions of this kind is sometimes called "focal fibrosis."

Acute Infarcts.—Terms Used to Identify Regions of Heart Involved by Infarction (Fig. 2): The "anterior" region was considered to involve the anterior wall of the left ventricle to the midportion of the anterior papillary muscle and also the anterior two thirds of the ventricular septum. The "posterior" region was the posterior wall of the left ventricle and included the posterior papillary muscle and the posterior third of the ventricular septum. The "lateral" region was designated as that portion between the anterior and posterior regions and, in essence, lay betwen the midportion of the papillary muscle in front and the lateral face of the posterior papillary muscle behind. The

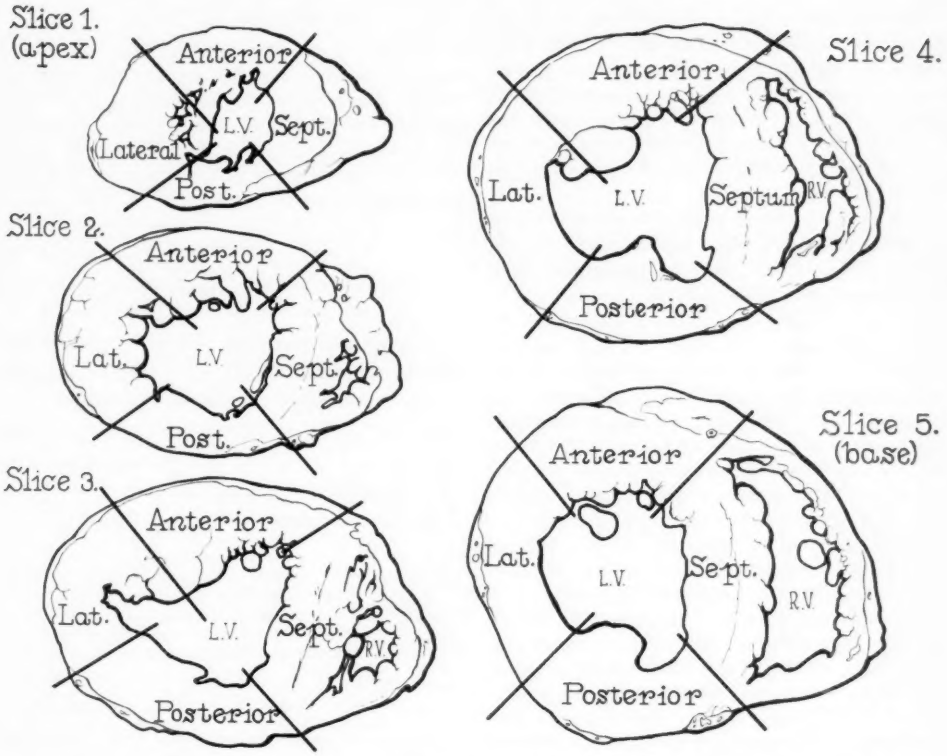

Fig. 2.—The myocardium viewed as a series of slices from the basal aspect toward the apical. The regions of the left ventricle and ventricular septum, representing the areas involved in infarction, are indicated between the various lines. (From Achor, R. W. P.: The Fate of Patients Who Have Survived Acute Myocardial Infarction, Thesis, Graduate School, University of Minnesota, Minneapolis, 1953.)

"septal" region, as the name implies, was restricted to the ventricular septum.

In some cases the acute myocardial infarct did not fall exactly into one of the regions designated. For example, the involvement in some acute anterior myocardial infarcts was beyond the anterior papillary muscle but did not include all of the lateral region. In other instances the anterior infarct might involve more than just the anterior two thirds of the septum. In general, however, the infarcts could be localized readily to one of the four regions named.

Terms Used to Identify Amount of Cardiac Muscle Involved by Acute Infarction: Acute infarcts which involved essentially the entire thickness of the left ventricle were described as "transmural." If infarction included only a portion of the thickness of the ventricle, the infarct was described as "subendocardial." Usually these latter infarcts were located in the endocardial half of the muscle. In some instances conglomerate necrotic tissue was noted, and in other instances the involved region contained alternating portions of acutely infarcted and noninfarcted muscle.

Determination of Type of Death

The clinical history and pathologic findings in each case were reviewed so that for each patient a type of death could be designated. The various types of death designated were as follows: myocardial failure, coronary failure, rupture of the heart, shock, and thromboembolic disease. The criteria for designating these types of death follow:

Myocardial Heart Failure.—When it was considered that the type of death suffered by a patient was one of myocardial failure, an attempt was made to determine whether the failure was predominantly of the right ventricle, predominantly of the left ventricle, or whether both ventricles appeared to contribute to the failure.

The term "predominantly right ventricular failure" was applied to patients with acute myocardial infarction whose clinical course was marked by evidence of congestive heart failure, either before or after infarction, and who had hydrothorax, often bilaterally, and ascites with dependent edema at necropsy. Passive congestion of the viscera was common in this group.

The category of "predominantly left ventricular failure" was applied to patients who had had acute myocardial infarction and whose clinical picture was characterized by one or more attacks of severe dyspnea; necropsy revealed pulmonary edema, the combined weight of the lungs often being in excess of 1,200 gm. Hydrothorax or ascites was not evident.

The term "combined right and left ventricular failure" was applied when necropsy showed pulmonary edema in addition to the conventional findings of right ventricular failure.

Coronary Failure.—This term is taken from the work of Blumgart, Schlesinger, and Zoll [2] and applied to our cases under the following circumstances: When the patient was convalescing from acute myocardial infarction, episodes of substernal pain occurred which were of a nature that might indicate that the patient was having recurrent acute infarction. These attacks of pain occurred usually days, and in some instances, weeks, after the time of acute infarction for which the patient was being hospitalized. Subsequently necropsy did not reveal any evidence of additional acute infarction or of acute coronary occlusion coinciding with the attacks of pain coming on during convalescence. Patients reported to have this condition did not show evidence of pulmonary edema, hydrothorax, ascites, or peripheral edema. These attacks of pain were considered to be expressions of myocardial ischemia which were not of such a degree as to cause myocardial infarction.

Another term that might have been applied to this phenomenon is "acute coronary insufficiency." It was not employed in our study, however, because, as used by Master's group,* it often implies the presence of necrotic muscle. Since we are concerned at this point with patients who did not have necrosis of muscle at the particular time of pain mentioned, we prefer to use the term "coronary failure" for the phenomenon described.

Rupture of the Heart.—This term was applied when death resulted from rupture of a free wall of the left ventricle with hemopericardium as well as from rupture of the ventricular septum.

Shock.—In cases in which death was attributed to shock the patient manifested pallor, sweating, weakness, and a systolic blood pressure of less than 100 mm. of mercury. Some of these patients presented this picture from the onset of myocardial infarction until death, but in others its appearance was delayed.

Thromboembolic Disease.—This category included both systemic and pulmonary thromboembolic phenomena but was limited to lesions the nature of which was considered sufficient to have played a major role in causing death.

* References 3 and 4.

Sex and Age of Patients

The ages of the 133 patients in this study ranged from 37 to 87 years, the average age being 65 years. There were 81 men (61%); their ages ranged from 37 to 87 years, and the average age at death was 63 years. The ages of the 52 women (39%) ranged from 49 to 87 years, and the average age at death was 68 years.

RESULTS

Location of Acute Myocardial Infarcts and Cardiac Muscle Involved

Sixty-eight patients (51%) had anterior myocardial infarction; 45 (34%) had posterior myocardial infarction, and 15 (11.3%) had infarcts of the lateral wall. In only three patients (2.3%) was the infarct limited to the ventricular septum. In only two of the 133 patients were two acute myocardial infarcts found. Both patients had had anterior infarction of 21 or more days' duration. In one patient the second acute infarct was posterior and of one day's duration. In the second patient the additional acute infarction was of two days' duration and was lateral.

Table 1.—*Correlation of Incidence of Previous Myocardial Infarction and Type of Acute Infarction in 133 Cases of Fatal Acute Myocardial Infarction*

Nature of Previous Infarction	Cases, No.	Transmural Acute Infarction	
		No.	Per Cent
None	53	45	85
Patchy	22	16	73
Conglomerate	58	32	55

In 40 cases (30%) the acute infarct was subendocardial, and in 93 cases (70%) it was transmural.

Correlation Between Incidence of Previous Myocardial Infarction and Type of Acute Infarction (Table 1)

Acute myocardial infarction was not associated with evidence of earlier infarction in 53 (40%) of the 133 patients. Transmural acute infarction, however, occurred in 45 (85%) of these 53 patients; this rate of incidence exceeded that for the entire group, which was 70%. Of the 22 patients having healed patchy infarction, 16 (73%) later had transmural acute infarcts; this rate of

TABLE 2.—*Type of Death in 133 Cases of Acute Myocardial Infarction*

Type of Death	Cases, No.	Per Cent of 133 Cases
Myocardial failure	57	43
Predominantly right ventricular	29	22
Predominantly left ventricular	17	13
Combined right and left ventricular	11	8
Coronary failure	31	23
Rupture of heart	20	15
Shock	12	9
Thromboembolic complications	8	6
Systemic	4	3
Pulmonary	4	3
Miscellaneous	5	4

TABLE 3.—*Incidence of Myocardial Failure Among 133 Patients with Acute Myocardial Infarction According to Presence or Absence and Location of Healed Infarction*

Healed Infarction		Myocardial Failure					
		Predominantly Right Ventricular Failure		Predominantly Left Ventricular Failure		Combined Right & Left Ventricular Failure	
Type	Cases, No.	Cases, No.	Per Cent of Healed Infarction	Cases, No.	Per Cent of Healed Infarction	Cases, No.	Per Cent of Healed Infarction
None	53	7	13.2	8	15	4	7.6
Patchy	22	9	40.8	1	4.5	..	....
Conglomerate	58	13	22	8	13.8	7	12
Total	133	29	....	17	....	11	....

incidence was close to the average of 70% for the entire series. In contrast, of the 58 patients having a conglomerate scar of healed infarction only 32 (55%) had transmural acute infarction, a rate of incidence significantly below the average.

INCIDENCE OF THE VARIOUS TYPES OF DEATH

Table 2 shows the number and per cent of patients who died from acute myocardial infarction according to the type of death. It will be noted that the three most frequent types of death are myocardial failure, coronary failure, and rupture of the heart, in that order of decreasing frequency. Thromboembolic complications causing death were present in a comparatively small number of patients.

FACTORS RELEVANT TO EACH TYPE OF DEATH

Myocardial Failure.—Of the 29 patients who died of predominantly right ventricular failure, 14 were men and 15 were women. Percentagewise, therefore, this type of death occurred about twice as frequently among women as among men. Two features appeared to be associated with the presence of predominantly right ventricular failure, namely, previous myocardial infarction and transmural acute infarction. From Table 3 it is apparent that among the 29 patients dying with predominantly right ventricular failure the incidence of healed infarction is significantly higher than is the absence of previous infarction. Moreover, of the 29 patients who had had right ventricular failure, 6 had had subendocardial infarcts (representing 15% of the 40 patients with subendocardial infarction) while 23 (representing 24.7% of the 93 patients with transmural infarction) had had transmural infarction. Age of patient and location of infarct did not appear to influence the occurrence of predominantly right ventricular failure.

In 17 patients the type of death was classified as predominantly left ventricular failure. The predominance of men in this group, 14 of the 17 patients being men, is striking. The ratio of 5 men to 1 woman is in contrast to the ratio of 1.5:1 for the entire series of 133 patients. Among the 11 patients with

combined right and left ventricular failure, the tendency for patients to have healed conglomerate infarcts was somewhat greater than for no previous infarction to exist.

It is of interest that among the 57 patients having myocardial failure 18 manifested the same type of myocardial failure before the occurrence of acute infarction as they manifested after myocardial infarction. Sixteen of them were in the group having predominantly right ventricular failure; 1 of the other 2 had predominantly left ventricular failure, and the other had combined right and left ventricular failure. Thirteen of these 18 patients had had previous conglomerate infarction; the 5 who had not had previous infarction had had calcific aortic stenosis or hypertension, each a feature that could explain the development of myocardial failure.

Coronary Failure.—Thirty-one patients died with the syndrome designated as "coronary failure." These patients were observed to have attacks of substernal distress again in the hospital while convalescing from their acute myocardial infarction. Pathologic study of the coronary arteries in these patients revealed recent coronary thrombosis in 19. Thrombosis in each instance coincided with the acute infarct as to age of the patient and location. In none of the 31 patients was there evidence of a coronary thrombus or of an infarct more recent than the infarct for which the patient had been hospitalized.

It will be recalled that two patients were shown at necropsy to have had acute infarcts in addition to and more recent than the infarct for which they were hospitalized. Acute occlusion of a coronary artery could not be correlated with the occurrence of the most recent infarction in either patient. In this way the two patients may be considered to have had coronary insufficiency with recurrent infarction. Since, however, neither of these patients manifested the syndrome of postinfarction pain, they are not included among the 31 patients whose deaths are considered to be of the type called "coronary failure."

The acute infarction of the 31 patients having recurring postinfarction anginal pain was subendocardial in 14 and transmural in 17, whereas of the entire group of 133 patients only 40 had subendocardial infarctions and 93 had transmural infarctions. Otherwise, the distribution of sex and age and the occurrence of previous infarction were not materially different among these 31 patients when compared with the entire group. Twenty-nine per cent of the patients with acute posterior infarction manifested postinfarction coronary failure, while 21% of those with acute anterior infarcts were so designated.

Rupture of the Heart.—Twenty patients died of rupture of the heart, 14 of the free wall and 6 of the ventricular septum, an incidence of rupture for the entire series of 15%. The predominance of women was striking. Whereas women constituted only 39% of the 133 patients in the entire study, among the 20 patients with cardiac rupture 15 were women and only 5 were men.

All of the infarcts resulting in rupture were of the transmural type, and in all but 1 of the 20 patients coronary thrombosis was associated with acute infarction of the myocardium. Among the patients with anterior or posterior infarction, the incidence of rupture was slightly lower than the incidence of rupture for the entire series, but the incidence of rupture among the patients with lateral infarction was significantly higher than for the entire series.

Among the 68 patients with anterior infarction rupture occurred in 8 (12%); among the 45 patients having posterior infarction rupture occurred in 6 (13%). Rupture occurred in 5 (33%) of the 15 patients having lateral infarction and in 1 of the 3 cases of septal infarction.

It has been stated that the use of anticoagulant therapy for acute myocardial infarction increases the incidence of cardiac rupture.[5] In view of this it was of interest to compare the incidence of rupture of the heart in patients treated with anticoagulants and those not receiving these drugs. For a review of this sort it seemed appropriate to study only the 93 cases with transmural infarction, since in the entire series there were no instances

of rupture complicating subendocardial infarction (Table 4). Also, since the difference in the incidence of rupture of the heart in women as contrasted to men was notable, it seemed proper to analyze separately the figures for each sex (Table 4).

Among the 93 patients with transmural acute myocardial infarction, only 23 had received anticoagulant therapy, usually bishydroxycoumarin (Dicumarol), in doses that had lowered the prothrombin activity to desired levels. The remaining 70 patients either did not receive anticoagulant drugs at all or, if they had received them, the period of administration was too short to accomplish desired degrees of deficiency of prothrombin activity. The latter patients and those who had not received anticoagulant drugs are considered, for the purposes of this paper, as patients who had not received anticoagulants. The main reasons for not administering anticoagulant drugs were as follows: the occurrence of death early after hospitalization and before there was time to give the drug; a tendency toward bleeding, such as after operation or from active duodenal ulcers, and severe renal insufficiency. In addition, in a certain number of patients with multiple complicating factors, such as diabetes and cerebrovascular disease with advanced mental changes, the acute infarction was not recognized clinically.

It will be noted from Table 4 that among the 70 patients with transmural infarction who were not treated with anticoagulant drugs 14 (20%) had cardiac rupture. Among the 23 patients with transmural myocardial infarction and with adequate anticoagulant therapy there were 6 cases of rupture, representing 26% of the group. The incidence of rupture was considerably greater among women whether or not anticoagulants had been given.

Twelve of the 20 patients having rupture of the heart were more than 69 years of age; 24 of the men, or almost half, were in this age group, but of these 24 men only 1 had cardiac rupture. On the other hand, 28 (or more than three fourths) of the women were in this age group; of these 28 women, 11 died of rupture of the heart. Among the patients with cardiac rupture there were more women (44%) dying in proportion to men (37%) in whom no evidence of previous myocardial infarction could be found, but the difference is not significant. The proportion of men and women having subendocardial and transmural types of infarction was about the same. While 12 of the 20 patients having cardiac rupture were patients who had the least cardiac hypertrophy, a third of both the men and the women were in this group. It is interesting to note that 16 (35%) of 46 women in whom blood-pressure readings were recorded after the onset of acute myocardial infarction had persisting hypertension, while only 14 (19%) of 73 men showed a tendency toward persistent hypertension. Only 2 (14%) of the 14 men in this category died of rupture of the heart, while 6 (38%) of the 16 women died of this complication. From these findings there is no ready ex-

TABLE 4.—*Incidence of Rupture of the Heart Among Ninty-Three Patients Dying with Transmural Infarction, Twenty-Three of Whom Had Received Anticoagulants and Seventy of Whom Had Not Received Such Therapy*

	Patients, No.	Rupture of Heart			
				Total	
		No.	Per Cent	No.	Per Cent
Anticoagulant Therapy					
Untreated					
Men	43	3	7	14	20
Women	27	11	40	..	..
Treated					
Men	13	2	15	6	26
Women	10	4	40	..	..

planation for the greater tendency for women to have rupture of the heart.

Shock.—Twelve patients, 10 of whom were men, died of shock. Six of these patients had persistent shock from the onset of the acute myocardial infarct to death, and three of these six suffered from shock after operation. Of the other six patients in whom shock developed as a terminal event, three had undergone surgical measures and a "silent" infarct had developed prior to operation. Shock had occurred in the other three cases one to three days after the patient was transferred to the Mayo Clinic for care, the infarct having developed one to two weeks previously. Age, cardiac muscle involved, or location of infarct did not appear to be factors in the development of shock, but 9 of the 12 patients who died from shock had had either a previous conglomerate infarct or a previous patchy infarct. This, however, is not significantly different from the incidence of healed infarction for the entire group.

Thromboembolic Complications.—None of the eight patients who died of thromboembolic complications had been treated with anticoagulants. Four of these patients had emboli occluding one or both main pulmonary arteries, and four had systemic emboli which could be considered to be the major cause of death. Included in this group were two patients with emboli to the internal carotid artery; one to the superior mesenteric artery and one to the femoral artery.

All four patients who died of systemic embolization had had previous myocardial infarction. Two of the patients dying of pulmonary embolism had transmural acute infarcts, and the other two had healed large conglomerate myocardial infarction. All of these patients were more than 60 years of age, and six of the eight patients were more than 70 years of age.

Among the 31 patients who had been treated with anticoagulants there were 17 (55%) who were found to have intracardiac thrombi; most of the thrombi were located in the left ventricle. The type of death of 8 of these 17 patients was classified as "myocardial failure." Six of the 17 patients had shown clinical evidence of cardiac failure, but the type of death was classified as follows: coronary failure, 3 instances; rupture of the heart, 2 instances; shock, 1 instance. Thus, 14 (82%) of these 17 patients showed evidence of myocardial failure at some time. Among the 102 patients not treated with anticoagulants, 45 patients had intracardiac thrombi demonstrated at necropsy; 28 of these 45 patients (62%) had evidence of myocardial failure either clinically or both clinically and pathologically; 17 patients showed no evidence of myocardial failure at any time.

TABLE 5.—*Incidence of Acute Deaths Among 133 Patients Dying of Acute Myocardial Infarction According to Type of Death*

Type of Death	Cases, No.	Acute Death	
		Cases, No.	Per Cent
"Coronary failure"	31	24	77
Rupture of heart	20	12	60
Myocardial failure, predominantly left ventricular	17	10	59
Myocardial failure, predominantly right ventricular	29	5	17
Pulmonary embolism	4	4	100
Myocardial failure, combined left and right ventricular	11	3	27
Other	21	0	0
Total	133	58	44

ACUTE DEATH AMONG 133 PATIENTS DYING WITH ACUTE MYOCARDIAL INFARCTION

In the previous portion of the paper the 133 patients of this study were considered from the point of view of the type of death on the basis of analysis of clinical and pathologic findings. Among these patients there were 58 whose death occurred unexpectedly, either suddenly or within minutes after a

sudden change in the course of the condition. Death in these cases was classified as "acute." This term should not be taken to represent a type of death, as used in the previous section. Most of the various "types of death" were represented among the 58 patients whose death was acute. The incidence of acute deaths among the 133 patients according to the type of death was determined. Table 5 shows the number of acute deaths in each of the categorized types of death and compares this number with the total number dying of each type of death. It becomes immediately apparent that most of the patients whose death was acute died of one of the three commonest types of death, that is, coronary failure, rupture of the heart, or predominantly left ventricular myocardial failure. In each of the four instances of pulmonary embolism death was acute.

COMMENT

The foregoing is an analysis of the cases of 133 patients having acute myocardial infarction, each of whom died in the hospital. Before any conclusions as to the behavior of coronary arterial disease can be drawn from this study the reader should reevaluate the methods of selection used in obtaining the 133 cases for study. As indicated, the cases analyzed represent 133 consecutive cases of acute infarction; pathologic examination was carried out in each instance, and the acute infarcts in each measured at least 2 cm. in one dimension. Therefore, cases of coronary artery disease were not included if the acute infarct was small. This study does not, of course, include evaluation of patients who were in the hospital with the same disease as the patients in this study but who survived their attacks of acute myocardial infarction. Moreover, the study does not include patients dying with acute failure of the coronary system in the absence of acute infarction; neither does it include patients with only healed infarction at the time of death. With these points in mind the cases herein analyzed may be evaluated better with respect to their position in the broad sphere of coronary arterial disease.

The study emphasized the high incidence of previous infarction among patients dying with acute infarction. Only 53 of 133 patients did not show evidence of some form of healed myocardial infarction, and the incidence of acute transmural infarction was greater among patients dying without previous infarction than for the over-all group. Another way of viewing the same phenomenon is that among these fatal cases the incidence of acute subendocardial infarction was higher among patients who had had previous infarction than for the entire group. One of the major factors contributing to the inclusion of patients who had had subendocardial acute infarction associated with healed infarction in a necropsy series, such as this, is cardiac failure. In some of the cases cardiac failure was present before infarction occurred, and in others, after.

In the analysis an attempt was made to indicate the type of death occurring in each of the patients. The evidence indicates that death from acute myocardial infarction, a type of death which we have designated as "coronary failure," represents the commonest single type of death. This condition is characterized by a syndrome of recurring pain after infarction, but without recurring infarction.

Also, it was common to find evidence of myocardial failure, "predominantly left," "predominantly right," or "combined right and left ventricular" in type. Of special interest was the relatively high incidence of cases in which myocardial failure existed prior to the onset of acute infarction. It is probable that in some such cases the circulatory dynamics peculiar to myocardial failure may in fact have been the precipitating cause of the acute myocardial infarction. Common underlying causes of failure preceding acute infarction were hypertension or previous myocardial infarction or both.

Rupture of the heart had occurred in 15% of the cases studied. In spite of indications in the literature [5] that anticoagulant therapy makes a patient vulnerable to rupture of the heart, the evidence from our material gives no support to such a conclusion. This study

indicated a strong tendency for women to have rupture of the heart as a complication of acute myocardial infarction.

The incidence of fatal embolic disease was relatively low. Four of the patients suffered major systemic embolism, and four, fatal pulmonary embolism, an over-all incidence among these fatal cases of 6% for major embolic disease. In this regard it is well to emphasize that the cases studied represented a selected group, in that all the patients died of their disease. Therefore, an indication as to the incidence of serious nonfatal embolic disease among patients surviving acute myocardial infarction cannot be given.

Mechanisms responsible for the various types of death are not readily forthcoming, although the syndrome of coronary failure is considered to represent attacks of myocardial ischemia. Nevertheless, the precipitating causes of such attacks cannot be ascertained. From this study it may be stated that these attacks cannot be considered to result from recurrent coronary thrombosis, since many patients did not have coronary thrombi and when they did have such lesions there was no evidence that would associate the attacks of recurring pain with any of the demonstrated acute occlusions of coronary arteries.

SUMMARY

Analysis is made of 133 cases in which the patients had acute myocardial infarction and died while in the hospital; in each case necropsy was performed. The age, sex, and type and location of the acute infarction and incidence of previous myocardial infarction were studied. The three major types of death were myocardial failure, which occurred in 43% of the cases; coronary failure, which occurred in 23%, and rupture of the heart, which occurred in 15%.

A factor influencing the occurrence of myocardial failure was previous myocardial infarction. Coronary failure, a term used to designate a syndrome of recurrent pain after acute infarction but without recurrent infarction, occurred in 23% of the patients. In this group the acute infarct was subendocardial in a greater number of cases than for the entire series. Rupture of the heart (of the ventricular septum in 6 cases and of the free wall in 14) was observed only in patients having transmural infarction. Women patients were predominant among those with rupture of the heart. The difference in the incidence of this complication among patients receiving anticoagulant therapy and those who did not receive such therapy was not significant. Major emboli occurred in 6% of the patients; half of these emboli were pulmonary, and half were systemic.

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Nutritional and Metabolic Aspects of Congestive Heart Failure

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Among the various aspects of the management of heart failure, nutrition has continued for many years to occupy a position of prominence. In cardiac decompensation, regardless of its etiology, alterations in cellular metabolism and physiology may rapidly influence alimentation and absorption of an adequate diet, the utilization of assimilated food elements, and the distribution of substrate, electrolytes, and water throughout the body.

The immediate problem in nutritional management is that of reducing the work load of the heart and preventing and eliminating abnormal water and sodium storage in extracellular space. The long-term problem is essentially that of maintaining the caloric, nitrogen, and accessory food factor balances at the minimum level of caloric intake to which the organism can be successfully adapted.

1. REDUCTION OF THE WORK LOAD OF THE HEART

Since cardiac output and the work of the heart are geared to the over-all metabolism of the individual person, a sharp restriction in the caloric intake initially is of benefit through the establishment of a state of undernutrition, which has been shown repeatedly, since the work of Benedict, to reduce the demands of the tissues for oxygen and substrate. At lower levels of energy demand by the tissues, cardiac work is decreased as much as one third of normal requirements.[1] The slowing of the heart rate with reduced basal metabolic rate affords longer periods of diastolic recovery for the hypertrophied myocardial fibrils. In heart failure there is a decreased flow of blood to the renal and hepatic circuits, shunting the effective circulating blood volume to other areas. Associated with a reduction in metabolic demands during transient undernutrition there may be improvement in the perfusion of liver and kidney as the energy needs of the body are reduced. Indeed, the benefits of subcaloric diets in patients with congestive heart failure were shown by Proger and Magendantz,[2] and the beneficial results continued as long as the lower weight was maintained.

In acute failure or myocardial infarction, the Karrell milk cure has been a popular dietary feature for several decades. It consists simply of the administration of milk, whole or skim, in amounts of 200 cc. four or five times daily for periods of four to seven days. This, together with restricted physical activity, frequently results in effective diuresis, improved myocardial efficiency, and relief of symptoms. This diet provides approximately 600 Cal. and 1 gm. of salt. With clinical improvement, the patient is given a diet restricted to 1200 Cal. per day, with frequent small easily digestible feedings being employed, during which energy expenditure is curtailed by the imposition of physical and mental rest. In the obese patient caloric restriction is maintained until adequate weight reduction has been effected. However, in the ambulatory, compensated patient, the protein and caloric allowances

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are gradually increased. Emphasis is placed upon the preparation of attractive and palatable protein feedings to assist the patient in consuming this type of food for which he may have little taste. Salt restriction is imposed to the level usually of 1 to 2 gm., which permits an adequate intake of the protein foods provided no salt is added in their preparation. Vitamin supplementation should be utilized from the very first day of the program.

Obesity: Obesity increases the work of the heart during physical effort because the body must move a larger mass. At rest, obesity may cause upward displacement of the diaphragm, resulting in a decrease in volume of lungs and change in position of the heart, increasing circulatory embarrassment. It is also reasonable to assume that the fatty infiltration of the myocardium seen in obesity may contribute to impairment of function of the heart. Therefore, if the patient is overweight, caloric restriction to bring his weight to normal or slightly subnormal is highly desirable.

Master and co-workers [8] studied the effects of a 1200 Cal. diet for a period of from two to seven months in obese patients who were otherwise normal. There was an average loss of 12% of their original weight. With the loss of weight there was an average loss of 30% in the cardiac output, a decrease of 34% in cardiac work, and an increase of from 10% to 27% in vital capacity. In our experience the obese patient in cardiac failure does not always show as great a benefit from a subcaloric diet as the nonobese patient. On the other hand, a reduction in weight is generally admitted to be a most effective measure in the management of coronary artery disease if obesity is present. However, it must be recognized that many of the younger coronary patients are not obese, as noted in the soldiers who developed coronary thrombosis in the Korean war theater. In this connection, the relatively high fat ration consumed by the troops may be a significant factor in the pathogenesis of coronary artery disease in this group.

2. PREVENTION AND ELIMINATION OF EDEMA

The pathogenesis of salt retention in congestive failure is a controversial subject. However, it is generally believed that a reduced glomerular filtration rate and increased tubular reabsorption of sodium is a major factor in salt retention. Impaired elimination of sodium results in retention of salt within the extracellular fluid, which increases storage of water, resulting in the development of increased venous pressure and edema.

Hormonal Influences.—Sodium retention and edema in heart failure cannot be fully explained by increased venous pressure or alteration in renal physiology. It seems that hormonal influences may be instrumental in salt retention in this condition. There have been several studies showing elevated levels of a desoxycorticosterone acetate (DCA)-like substance in the urine of patients with congestive failure.[4] Recently the sodium-retaining corticoid has been identified as aldosterone.[5] And there is evidence that adrenolectomized dogs in experimental congestive failure fail to develop salt retention and ascites.[6] Thus, the significance of adrenal cortex activity in the pathogenesis of salt and fluid retention in congestive failure is impressive. It has also been suggested that water retention in congestive failure may be due to an augmented release of antidiuretic hormone (ADH) from the neurohypophysis in response to stimulation by osmoreceptors and volume receptors.* However, the slight incidence (18%) of an augmented antidiuretic activity of the plasma in patients with congestive failure is probably to be attributed to the degree of nonspecific stress produced by the patient's physiological derangement or to the "character of the psychological response to the presence of his illness." [9]

A significant experimental finding is that animals with mild right-sided valvular lesions without edema or ascites show a decreased sodium excretion following a saline load.[10] Pertinent to this is the clinical observation that patients who have become compensated after a previous attack of con-

* References 7 and 8.

gestive failure show impaired sodium excretion. Warren and Stead [11] were able to produce signs and symptoms of cardiac failure by adding an excessive amount of salt to the diet of such compensated patients. Logically, then, a salt-restricted diet as an adjunct to therapy of congestive failure has found wide acceptance. Restriction of salt to a level less than urinary output will decrease edema; restriction of water alone is ineffectual.[12] Salt restriction will permit water intake up to 2500 to 3000 cc. daily, affording the patient more comfort by relief of thirst and dehydration. However, one must vary restriction of salt with the severity of heart failure. In mild cases, simply avoiding salt at the table and restricting its use in cooking will prevent edema formation. In moderate cases of heart failure, a diet providing 1.5 to 2 gm. of salt daily with adequate fluid ingestion will usually prove effective in increasing diuresis. Not all patients will respond alike to restriction of salt. Some patients with little myocardial reserve often fail to become free of edema and will manifest pulmonary congestion despite digitalis, diuretics, and moderate sodium restriction. In such patients, the sodium in the diet should be reduced to 0.2 gm. (0.5 gm. of sodium chloride) daily. In addition to restriction of sodium, Schemm † and others have recommended a neutral or slightly acid ash diet as beneficial through the increased formation of metabolic acids which combine with sodium in the body and which are excreted through the kidneys. The excretion of sodium with metabolic acids will result in a decrease of extracellular sodium and fluid, thus enhancing diuresis. Owing to its unpalatibility, however, and the need for extreme care in its preparation and rigid supervision of its employment, the applicability of this regimen is limited to selected cases; thus, where is can be used, the low-salt, acid-ash, and fluid ad libitum treatment of congestive heart failure proves most effective. Patients who cannot be maintained on salt-restricted diets may require mercurial diuresis, ion-exchange resins, or carbonic anhydrase inhibitors.

Low-Salt Syndrome.—Recently attention has been drawn to the danger of excessive salt restriction when mercurial diuretics are administered. The low-salt syndrome may develop in an occasional patient with congestive failure in whom salt depletion has been produced by a drastic salt restriction and mercurial diuretics in the presence of a preexisting impairment in the resorptive function of renal tubules. This syndrome can be recognized by a decrease in urinary output and the increase in edema; as the depletion progresses, the patient shows apathy, lethargy, nausea, vomiting, weakness, and muscle cramps. In the case of hyponatremia as well as hypochloremia, sodium chloride either orally in tablet form or as 3% to 5% solution intravenously may bring about prompt improvement. Diuresis may be established and symptoms of salt depletion abate. Low-salt syndrome is of clinical importance; for when unrecognized and not properly treated it may prove fatal.‡

3. MALNUTRITION

In the presence of chronic heart failure, malnutrition develops in many patients and is manifested by atrophy of the muscles of the pectoral region and upper extremities. Edema may mask emaciation elsewhere. Malnutrition may aggravate cardiac failure of other causes and may be one factor in the unresponsiveness to classical types of therapy.

The maintenance of nutritional balance of the chronically ill patient with congestive heart failure centers around (*a*) replacement of existing depletion of body stores and (*b*) restoration of deranged myocardial intracellular metabolism. Cardiac reserve is dependent to a great extent upon the physiologic integrity of heart muscle. The latter is dependent upon an adequate supply and utilization of oxygen, protein, carbohydrate, vitamin, and minerals.

Replacement of Depleted Body Stores.—The depletion of body stores of protein and

† References 13 and 14.

‡ References 15 and 16.

of other essential nutrients has been demonstrated as a cause of nutritional heart failure. Such depletions have been noted in long-standing congestive failure of valvular, hypertensive, and arteriosclerotic etiologies. Because of the detrimental effect of nutritional deficits of protein and certain vitamins upon cardiac function, the maintenance of an optimal nutritional status is a prerequisite in the management of the patient with chronic cardiac disease. In addition to the structural factors, such as coronary arteriosclerosis, myocardial fibrosis, and hypertrophy, there are other important problems in supplying adequate nutriments to the heart muscle and other tissues in heart failure. Changes in cellular metabolism are observed, as manifested by alterations in sodium, potassium, nitrogen, and water concentrations within the cells.§ It is likely that anoxia is an important basic condition leading to shifts in electrolyte concentrations which have been described.

Causes of Loss of Body Protein.—The chief cause of hypoproteinemia is malnutrition. The basic difficulties are in the absorption and utilization of foodstuffs. The reduced appetite limits the actual intake of food, particularly meat and other protein sources. The assimilation of digested foods is impaired by the reduced transport rates in the absorption pathways of the gastrointestinal and portal systems. The dynamic activity of the gastrointestinal mucosal cells may be affected by an alteration in electrolyte concentrations and by anoxia. Furthermore, the rate of utilization of the absorbed nutrients by the liver is impaired owing to the alterations in liver function—a common finding in heart failure.[19] Other contributing factors are proteinuria and loss of protein which occurs when ascites or pleural effusions are frequently tapped. That protein utilization is actually decreased in congestive failure was shown by Armstrong and associates.[20] They found the rate of protein turnover in congestive failure to be strikingly prolonged. In similar studies, employing radioactive-iodine-labeled tyrosine, the rate of utilization of this amino acid has been shown to be decreased in cardiac failure patients as compared with that of control subjects.‖ Such alterations in protein and amino acid metabolism may increase the refractoriness of these patients to the treatment. Our efforts should therefore be to maintain the blood and tissue protein at a normal level. This calls for high protein intake with a minimum of salt.

Thiamine.—The status of thiamine nutrition was investigated in 35 patients admitted to Philadelphia General Hospital in congestive heart failure, by means of a thiamine-loading test using 0.35 mg. of thiamine per square meter of surface area. The mean thiamine excretion in four hours was 40.6γ in cardiac patients and 139.5γ in a control group.[21] The thiamine and cocarboxylase content of the myocardium of patients dying of congestive failure was compared with the concentration of these substances in hearts obtained from noncardiac patients at autopsy. Significantly lower quantities of thiamine and cocarboxylase were found in the cardiac group.[22] Finally, the levels of blood pyruvate following glucose load and exercise were found to be elevated in 22 patients with congestive heart failure. The mean pyruvic acid level was 2.01 mg. per 100 cc. (0.89 to 5.04 mg. per 100 cc.). The range of normal controls for serum pyruvic acid was 0.5 mg. to 1.6 mg. per 100 cc. Following intramuscular administration of thiamine (50 mg. daily in seven patients) for seven days the levels of pyruvate were decreased during the course of the test.[23] Possibly one of the factors involved in hypothiaminosis in congestive heart failure is the use of mercurial diuretics. In nine patients receiving these agents we found a 24-hour urine thiamine content of 403.2γ; during the control periods prior to the administration of mercurials the output was 135γ per 24 hours, corresponding to levels found in normal persons not receiving vitamin supplementation.[24] The reduction of tissue thiamine in congestive heart failure

§ References 17 and 18.

‖ Shuman, C. R.; Robbins, R., and Wohl, M. G.: Rate of Utilization of Labeled Tyrosine in Congestive Heart Failure, unpublished data.

may interfere with cellular metabolism because the coenzyme cocarboxylase (thiamine pyrophosphate) derived from thiamine is necessary for oxidation of pyruvate to acetate. The final combustion of the latter with liberation of free energy in the heart muscle occurs via the Krebs tricarboxylic acid cycle.[25] Animal studies indicate the importance of thiamine, biotin, and pantothenic acid in cardiac muscle metabolism.¶ A possible effect of deranged myocardial metabolism may be that of further reducing cardiac efficiency and of rendering the maintenance of compensation more difficult. On the other hand, Bing and others have shown that the myocardium is capable of oxidation of noncarbohydrate nutrients—fat, ketones, and amino acids. The work of Bing suggests that heart incompetency is primarily the result of an impairment of the ability of the myocardium to convert energy derived from substrates into mechanical work.[29] Katz and others [30] are of the opinion that "the primary defect is in the release of energy and that the ability to employ this energy for work is not primarily impaired in all instances of heart incompetency." The question remains open as to whether in the more resistant later phases of heart failure, due to hypertension and chronic valvular disease, the metabolic defect of low capacity for energy formation as well as impaired energy utilization is involved.

Vitamin supplementation has been used orally and parenterally in most of the patients examined in the thiamine excretion studies performed by us. It has been recommended that 100 mg. of thiamine daily be given to patients with congestive failure. Our present investigations indicate that there is no advantage in the administration of thiamine in quantities larger than 10 mg. daily, parenterally, in correcting the subclinical deficiencies detected by the loading-test method.[30a]

The patients in congestive heart failure found to be resistant to the usual therapeutic measures have not always been benefited by efforts at protein and vitamin replacement. Whether failure to respond reflects irreversible biochemical and morphologic changes in the myocardium or the necessity for supplying additional factors (cocarboxylase, adenosine triphosphate [ATP]) is a subject for further investigation. Long-term observations on patients seen in early phases of heart failure with special attention to the maintenance of the nutritional status have not been made. However, the problem of overcoming anorexia, absorption and utilization defects, and alterations in cellular metabolism are formidable obstacles confronting the physician concerned with the nutritional aspects of cardiac disease.

Potassium Disturbance.—One of the significant manifestations of congestive heart failure is the changes in electrolyte concentration and a change in water balance in the two large body fluid compartments. Whether inherent changes in intracellular metabolism or depletion of body potassium is the primary factor leading to increase in intracellular sodium and water is not established.[31] There is biochemical evidence that a reciprocal relation exists between K^+ and Na^+ and that during potassium depletion the Na^+ content of cardiac muscle as well as skeletal muscle increases. These intracellular ionic shifts may result in an inhibition of enzyme systems such as those regulating the production of high-energy bonds, a condition necessary for the preservation of cellular K^+ and the extrusion of Na^+ from the cells. (In this connection, it is of interest that Cannon [32] observed myocardial necrobiosis in the growing rat deficient in K^+. Whether the same findings obtain in man is not known.)

The use of potassium salts in the dietotherapy of congestive heart failure has gained increasing prominence. In three patients with congestive failure resistant to mercurial diuretics electrolyte study of muscle biopsy specimens showed a large deficit of potassium and overhydration of cells.[33] One of these patients was treated with high potassium intake and the maintenance of digitalis but without mercurials. This resulted in prompt diuresis and

¶ References 26-28.

considerable clinical improvement. This is a good example of the influence of nutritional deficits upon organ function and drug therapy. Potassium in the form of the chloride salt or organic salts (Triplex) in doses of 3 gm. daily may be sufficient. It is necessary to be certain that renal function is not impaired, that oliguria is absent, and that hyperpotassemia is not present when such therapy is employed.

Dietotherapy—Therapeutic Salt-Restricted Diets.—The basic foods required in the diet to provide adequate nutrients must receive primary considerations: Milk, 1 pt.; meat, 5 oz.; vegetables, two servings; fruit and fruit juices, three servings; carbohydrate and fat to fulfill caloric needs. In order to restore depleted protein levels, it is necessary to increase the protein component by adding meat servings. The diet should contain proteins of high biologic value in quantities at least 1.5 gm. per kilogram of normal body weight as soon as diuresis begins. The caloric requirement of the diet is based upon the body weight of the patient with respect to the desired weight. One may encounter hypoproteinemia in overweight persons. In these instances, we have encouraged high-level protein feedings (1.5 to 2.0 gm. per kg. body weight) with restriction of carbohydrate and fat. There is evidence to indicate that protein repletion can occur despite caloric restriction under these circumstances, the energy requirement being satisfied by endogenous fat sources.[33]

After the dietary requirements for protein, accessory food factors, and calories are fulfilled, the problem of sodium restriction must be solved. By use of the following measures the sodium intake can be restricted to an average of 0.6 to 0.8 gm. (1.5 to 2 gm. of salt daily): Avoid canned foods unless prepared without salt. Use unsalted breads and fats. Avoid frozen peas and lima beans; avoid fresh beets and celery. Use no preserved foods, meats, fruits, flour mixes, or relishes containing salt. Cured meats are heavily salted and should be avoided. Coffee and instant coffee are low in sodium (0.2 to 1.6 and 0.2 to 0.9 mg. per cup, respectively) and may be permitted in moderate amounts. Seafood—clams, shrimp, halibut, sardines, salmon, tuna—is rich in sodium and should be excluded. Fresh-water fish may be permitted. For more strenuous salt restriction, to the level of 200 to 400 mg. per day, the use of a sodium-free milk such as Lanolac or Lesofac is necessary. Salt-free bread (matzos) and unsalted butter are to be used. For high-level protein feedings with sharp sodium restriction various low-sodium meat and milk products must be employed. Several salt substitutes such as Co-Salt, Neocurtasal, and Diasal may be recommended for flavoring. These contain ammonium and potassium chloride and may be used in the absence of serious renal insufficiency. Lemon juice, dry mustard, and pepper may also be employed for the seasoning of food. If the basic foods are included in the diet, vitamin supplementation may not be required. However, if diuretics are necessary in the management of fluid retention, the administration of a balanced vitamin preparation orally, or preferably parenterally, is recommended. To prevent potassium depletion the diet is supplemented by the addition orally of organic potassium salts (oral potassium Triplex, 2 teaspoonfuls (9.8 ml.) three times daily).

Attention to these details should provide a diet adequate to accomplish the objectives of the dietary management of heart disease. However, our ability to influence the defects of absorption and utilization of ingested foodstuffs has not improved. Further study of these aspects of the problem is indicated.

SUMMARY

The ability of the heart to fulfill its function in maintaining the circulation can be influenced materially by diet. By appropriate dietary regulation using subcaloric feedings in acute failure, the work of the heart is reduced, thereby increasing blood flow, lowering the blood pressure, slowing heart rate, increasing vital capacity, and inducing diuresis. The restriction of dietary sodium is a basic step in avoiding fluid retention due to

impairment of renal sodium excretion. Effort should be made to assure adequate potassium tissue stores by the periodic administration of potassium salts to chronic failure cases. Supplemental vitamin therapy is required as shown by the presence of low tissue vitamin stores in heart failure and the high rates of vitamin excretion during diuresis. The assurance of an adequate protein intake is urgently needed in the hope of avoiding the evidences of protein malnutrition which eventually appear in so many of these patients.

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Pulmonary Embolism

A Review with Emphasis on Clinical and Electrocardiographic Diagnosis

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Pulmonary embolism is a not uncommon complication in patients hospitalized for other medical and surgical diseases. The autopsy incidence of pulmonary embolism is much higher than that anticipated by clinical diagnosis.* For these reasons we have reviewed the cases of pulmonary embolism that have occurred at Montefiore Hospital during the past five years. Certain clinical features, not sufficiently emphasized in the medical literature, were discovered to occur in a high incidence. The electrocardiogram, a good collateral aid in the diagnosis of pulmonary embolism, is usually not obtained early enough, often enough, nor in a serial fashion.

Sixty-seven records were examined, and of this group 62 cases were selected, because in 5 instances the available data were inadequate for proper analysis. Of the 62 cases, 33 were autopsied and in 29 the patients recovered. Forty-nine were medical cases, and 13 were surgical. The complicating medical features in the patients selected were as follows: congestive heart failure, 37; myocardial infarct, 8; pneumonia, 2; cerebral vascular accident, 1; thrombophlebitis, 1. Pulmonary embolus complicated the following surgical procedures: herniorrhaphy, 4; colonic resection of carcinoma, 4; cholecystectomy, 2; suprapubic cystotomy, 1; orchiectomy, 1; cataract, 1. Of the 33 autopsied cases of pulmonary embolism, 25 medical and 8 surgical, only 9 were correctly diagnosed before death. Forty-one patients had electrocardiograms, and 36 had chest x-rays.

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The pathology of pulmonary embolism can be classified under two chief categories. These are (1) massive, fatal pulmonary embolism without pulmonary infarction and (2) pulmonary embolism with pulmonary infarction. In those instances of massive, fatal pulmonary embolism without pulmonary infarction, the main stem of the pulmonary artery and the larger branches are blocked by a clot that is twisted, cylindrical or thickened, fragmented or intact, varying in length from 15 to 30 cm. Statistically, the cylindrical clots take origin in the femoral and external iliac veins. The thicker masses with a large number of tree-like branches usually arise in the bed of the internal iliac vein, originating most frequently in the uterine veins. The embolus may show valve markings and small broken branches which can be matched with the valves and tributary veins of the leg vessel of origin. Because death is usually sudden, there is inadequate time for pulmonary infarction and secondary pathological changes to appear. The lungs are only slightly edematous and hyperemic. The right ventricle is usually dilated. Infarction of the lung secondary to pulmonary embolism occurs in a high incidence. In our series of 33 autopsied cases this lesion resulted in 24 instances. Usually the infarct is pyramidal or wedge-shaped, with its base directed pleurally and its apex at the site of vascular occlusion. The very fresh infarctions, however, are not so sharply defined, but merge with the surrounding pulmonary parenchyma through a zone of edema and fading hemorrhage. During the first few days, the infarct is pink and soft. Blood oozes from the moist cut surface. Micro-

scopically, there is extravasation of blood into the alveoli of these "red" infarcts. After the first stages the infarcted area becomes progressively firm and dark until organization is completed. Microscopically, red cells become enmeshed in a fibrinous network and necrosis of the alveolar walls occurs. Fibroblasts and young capillaries progressively penetrate the necrotic area. A region of fibrinous pleuritis, resulting in fibrous pleural adhesions, often marks the site of a previous pulmonary infarction. In the course of time many infarcts will apparently disappear, but if the lung is carefully inflated and diligent search made small peripheral scars often indicate the site of the old pulmonary infarction. Furthermore, in most lungs in which infarction develops, there is a background of chronic passive congestion. This pathologic finding is supported clinically, for chronic passive congestion of the lungs occurred in 37 of our 62 cases of pulmonary embolization. Some authors refer to a subdivision of this second major group as "incidental pulmonary emboli." [3] Instances of the latter are seen in patients suffering from long-standing debilitation, as in advanced carcinoma. "Incidental," as used here, means that the pulmonary embolus found at autopsy was not the major cause of death. However, by blocking the pulmonary circulation, these small emboli probably contribute to the cause of death. These soft and friable emboli are firmly impacted in the arterial branches. The surrounding lung parenchyma is hyperemic and edematous. Another controversial subdivision of this large pathologic group consists of "thrombosis in situ." These infarcts are presumably produced by thrombosis within the lumen of the pulmonary veins or arteries. This lesion, too, is often classified as an "incidental" pathologic finding. It must be remembered, however, that not all clots in the pulmonary arterial tree are necessarily thrombi. They may be organizing emboli. Another similar, more important group has been described recently by Castleman and his associates. Recurrent, usually unrecognized emboli can lodge in many large and small arterial branches, ultimately resulting in serious obstruction to the flow of blood in the lungs and the clinical picture of progressive, intractable congestive heart failure and cor pulmonale of unknown cause.[2] At autopsy, organization and partial recanalization of the involved vessels is seen, with no associated extensive areas of infarction.

Pulmonary embolism, which imposes an obstruction in the course of the pulmonary circulation, is an entity which lends itself to analysis of its dynamics and pathologic physiology.[4] It is a commonly accepted fact, supported by experimental evidence, that the degree to which the pulmonary circulation is compromised will generally determine the symptomatology when a pulmonary embolus strikes. It is true, however, that occasionally a patient will die suddenly and a relatively small embolus will be found at autopsy. Then one must invoke a reflex mechanism, probably vagal, as a cause of death. Generally, simple dynamics can explain the signs and symptoms that result from a pulmonary embolus (Table). When an obstruction is interposed between the two contracting ventricles, three groups of symptoms may result. The first will include those symptoms due to insufficient flow from the left ventricle, resulting in peripheral circulatory failure or shock. The second group of symptoms will arise directly beyond the point of obstruction. In this situation, the signs and symptoms of pulmonary infarction will result. A third group of symptoms will be a reflection of the right ventricular failure.

Incidence of Signs and Symptoms of Pulmonary Embolism

	Per Cent of Cases
Apprehension and related mental symptoms..	60
Pulmonary infarction.....	58
Peripheral circulatory collapse.....	50
Right heart failure.....	45

When the left ventricle pumps an inadequate amount of blood into the systemic circulation, peripheral circulatory failure and shock-like symptoms and signs arise. The shock syndrome, as manifested by tachycar-

dia, hypotension, pallor, cool clammy skin, and diaphoresis, occurred in 50% of our series of patients. The second group of symptoms, those of pulmonary infarction, due to obstruction in the flow of blood to the lungs, occurred in approximately 58% of our cases. Thirty of this group complained of severe dyspnea and chest pain. Cough and hemoptysis were noted in 10 instances. Physical signs of pulmonary infarction including rales, rhonchi, pleural friction rub, consolidation, and pleural effusion occurred in 37 patients. X-ray corroboration of the presence of pulmonary infarction was seen in 19 cases. The roentgenographic aspects of pulmonary infarction are variable and nonspecific.[5] The x-ray appearance depends upon whether an infarction is complete or incomplete. The complete infarction may produce any one of the following abnormal x-ray densities, depending on location and number of lesions: pyramidal, oval, round, irregular, or triangular. There is some predilection for the right lower lobe. The area of infarction is almost always in contact with one or more pleural surfaces, and the long diameter of the shadow is parallel to the pleural surface. There are several other indirect x-ray signs of pulmonary embolization, consisting of costophrenic angle clouding, hilar vessel accentuation on the side of the lesion, a prominent pulmonary conus, diaphragmatic elevation of the affected side, and pleural effusion. Evidence of incomplete infarction may be changing transverse or oblique sharp lines on a chest x-ray that previously was negative or a sharp area of radiolucence. Fluoroscopy many times is more valuable than x-ray in corroboration of the clinical impression of pulmonary embolization. Signs of pulmonary embolization detected on the fluoroscopic screen include (1) hyperactivity of the pulmonary arterial system, (2) an elevated and inactive diaphragmatic leaf on the affected side, (3) areas of atelectasis, (4) a zone of pulmonary avascularity, (5) in the acute phase, surrounding of the involved pulmonary artery segment by a hazy infiltration area, due to edema. This may be seen to subside if infarction does not occur. From this brief review of the roentgenologic aspect of pulmonary embolization, one can see that the x-ray contribution to correct diagnosis is variable and many-sided. There is no specific picture on x-ray, as many texts imply. The "wedge-shaped" shadow is neither classic, typical, nor commonly encountered.

Changes occur in the right side of the heart due to the sudden obstruction imposed to the flow of blood from the right ventricle. The right ventricle dilates and rotates, producing a group of symptoms and signs characteristic of right heart failure. Cervical vein distention and enlargement of the liver occur, but peripheral edema is rarely seen, because the patient is usually bedfast. Signs and symptoms of right ventricular failure were present in 45% of our cases. However, 37 of our patients had a background of congestive heart failure on admission. Presumably, a large percentage of these had borderline or overt right heart failure. On this basis, any dogmatic expression of incidence of right heart failure is subject to criticism.

There is a fourth group of symptoms that may occur with a pulmonary embolus. These symptoms are nonspecific and are apparently not exclusively related to the obstructive dynamics imposed by the blood clot. On careful analysis of our case records we were particularly impressed with the high incidence of these symptoms and carefully analyzed both house staff and nursing notes for further evidence of their significance. In 37 instances we found expressions of apprehension and related mental symptoms, preceding the evidence for a major pulmonary embolus. Expressions of anxiety such as the following were repeatedly in evidence on our records: restless, apprehensive, irritable, uncomfortable, nervous, twitching, carphologia, excited, combative, argumentative, "concerned about myself," noisy, muttering incoherently to self, confused, disoriented, depressed, dying, "want to die," despondent, unhappy, emotional, crying, drowsy, lethargic, "sinking feeling," visual hallucinations. Previous investigators [6] have mentioned apprehension in their clinical analysis of pulmonary embolization, but in their reports this was usually a

concomitant of the picture of shock. One of Murnaghan's original case reports on acute cor pulmonale describes a patient who was "nervous and restless" before the major catastrophe, but these authors attached no special significance to these complaints.[7] The mechanism of this symptom complex is not immediately apparent. It would seem entirely feasible that a small fragment of thrombus might be lodged in a branch of the pulmonary arterial tree, setting up a reflex stimulation of the autonomic nervous system. Also, the pathways of the pituitary-adrenal stress reaction might be activated, as a result of the threat of a dissolution of the body homeostasis. An alternate explanation for this nonspecific response could invoke cerebral anoxia, secondary to decreased cardiac output. The argument for cerebral anoxia as a mechanism in the production of premonitory mental symptoms in pulmonary embolism is borne out by the occasional case of proved pulmonary embolism in which hysteria and convulsive episodes coexist. Although the mechanism for production of anxiety and its concomitants is not clear, the following point is definite. The incidence of these nonspecific symptoms, 60% in our series, is significantly high, and apprehension often precedes the major catastrophe of pulmonary embolism. When these symptoms are present, the clinical impression of pulmonary embolism should be entertained, particularly in those medical and surgical patients whom we know are particularly vulnerable to thromboembolism. With a high index of suspicion, triggered by the patient's expression of anxiety, prophylactic measures can be instituted at once. Another manifestation of stimulation of the autonomic nervous system is interference with sphincter control, including the urge to defecate. Twenty of our patients experienced this symptom. The 10 patients who complained of the uncontrollable, overpowering urge to defecate died abruptly. Of these, eight were autopsied. Five showed massive occlusion of a large pulmonary vessel, which resulted in sudden death without time for infarct formation. In only three members of this group were pulmonary infarctions found. Ten patients were incontinent of urine and feces for variable periods before death. Seven of these were autopsied, and all were shown to have pulmonary infarction. Presumably, the urge to defecate resulted when there was sudden occlusion of a large pulmonary arterial vessel, while incontinence appeared to result when there was more gradual occlusion of the pulmonary vascular tree with adequate time for subsequent infarct formation. As so frequently occurs with diseases above the diaphragm, pulmonary embolism may also cause symptoms referable to the gastrointestinal tract. It was not uncommon for patients in our series to complain of nausea, vomiting, and epigastric distress, described as "butterflies in my stomach," "sickening feeling in my stomach," and just generalized epigastric discomfort. Hiccoughs on occasion accompanied the above symptomatology.

It is apparent to us that while a small pulmonary embolus may not cause all the classic symptoms and signs of pulmonary infarction it may alert us to forthcoming events, by the reflex mechanisms already cited. We suggest that, when the clinical impression of impending major pulmonary embolism is warranted, intensive search for the site of thrombus formation be made and the following diagnostic procedures be accomplished: (1) procurement of an electrocardiogram and chest x-ray, (2) routine measurements of thigh and calf girth at various levels at least daily, (3) employment of the Lowenberg blood pressure cuff technique, which consists of blood pressure localization of the probable site of thrombus formation in the extremities.[8]

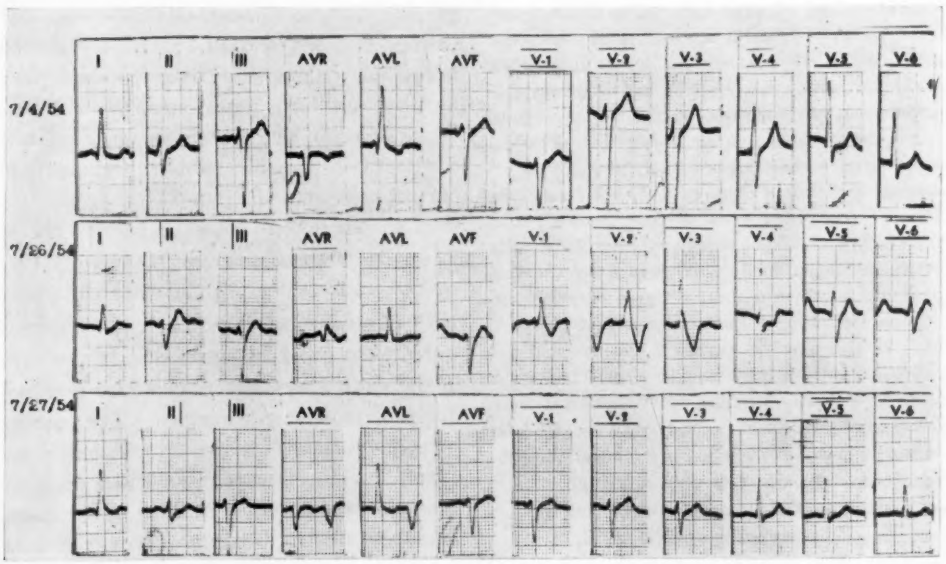
An embolus that lodges in the pulmonary artery or its branches can impose a dynamic effect on the right heart, as described above. This effect may be reflected in the electrocardiogram by the pattern of acute cor pulmonale. McGinn and White, in 1935, were the first to crystallize the pathognomic features of the electrocardiographic diagnosis of acute cor pulmonale.[4] Subsequently this pattern was modified by Murnaghan, McGinn,

and White.[7] With the advent of precordial and augmented unipolar extremity leads, various groups of investigators still further clarified the electrocardiographic pattern of acute cor pulmonale.† The changes commonly seen in the total electrocardiographic expression of the pulmonary embolism are (1) the development of an S-wave in standard Lead I; (2) depression of the ST-segment in standard Leads I and II, associated with "staircase ascent" of the ST-segment in other leads; (3) flattened to inverted T-waves in standard Leads II and III; (4) the appearance of a Q-wave in standard Leads III and aV_F; (5) presence of tall, peaked P-waves in standard Leads II and III; (6) various degrees of intraventricular block of the right bundle branch system and even the development of the right heart strain pattern, with inversion of T-waves in one or more precordial leads; (7) clock-wise rotation of the heart, resulting in a movement of the transition zone to the left in the precordial leads; (8) development of a vertical electrical position; (9) evidence for superimposed coronary insufficiency. Not all of the above electrocardiographic evidence need be present to consider the diagnosis of pulmonary embolism. Since these electrocardiographic changes are probably dependent primarily upon the amount of dynamic obstruction, it is obvious that when the degree of obstruction is not sufficiently great only minor electrocardiographic changes may result. Although there is a difference in opinion as to the incidence of positive electrocardiograms in pulmonary embolism, almost all investigators agree that frequent serial tracings begun early are necessary to demonstrate these ofttimes transient changes. The following case clearly illustrates these transient changes.

† References 9-11.

M. S., a 69-year-old white man, entered the hospital on July 26, 1954, complaining of a cough, fever, and severe pain, localized to the left lower costal margin and aggravated by respiration. He had been confined to bed for several months prior to admission because of rheumatoid arthritis and congestive heart failure. An electrocardiogram (Fig. 1) on admission revealed evidence of acute cor pulmonale after comparison with previous tracings. The next day, July 27, 1954, there were signs of left-sided pleural effusion on physical examination. A chest x-ray on July 27, 1954, confirmed the presence of a left pleural effusion. An electrocardiogram on July 27, 1954, demonstrated a complete return to the horizontal position and absence of the previous acute

Figure 1.



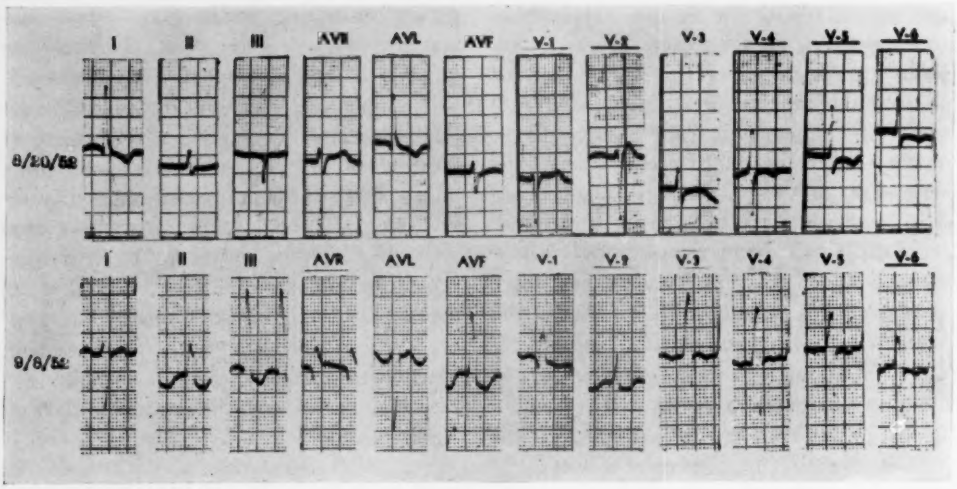


Figure 2.

cor pulmonale picture. Despite a prolonged convalescence, complicated by development of a left ureteral calculus and subsequent ureterolithotomy, the patient was discharged from the hospital in an improved state on Sept. 19, 1954.

Congestive heart failure is a frequent background for the development of pulmonary embolism with resultant pulmonary infarction. The following case demonstrates the electrocardiographic picture that can occur in such situations.

B. H., a 65-year-old white woman, entered the hospital on Aug. 19, 1952, suffering from congestive heart failure on an arteriosclerotic-hypertensive basis. She never responded fully to appropriate therapeutic measures. Dyspnea and extreme restlessness, out of proportion to the degree of congestive heart failure present, persisted. Physical examination revealed evidence of parenchymal infiltration and pleural effusion in the left lower lung lobe. An electrocardiogram on Aug. 20, 1952 (Fig. 2) revealed atrial fibrillation and left ventricular strain with digitalis effect. A chest x-ray corroborated the presence of the left lower lung lobe infiltration and associated pleural effusion. On Sept. 7, 1952, at the time of increased dyspnea and apprehension without chest pain, an electrocardiogram disclosed a supraventricular tachycardia and signs of acute cor pulmonale. A chest x-ray one day later revealed a new area of pulmonary infiltration in the right lower lung lobe. The patient died on Sept. 8, 1952. Pulmonary infarctions were found in both lower lung lobes on postmortem examination.

There are pitfalls in the electrocardiographic diagnosis of acute cor pulmonale. The more important ones are the following. The presence of a Q-wave and inverted T-waves in Leads II, III, and aVF is usually diagnosed as a posterior myocardial infarction. However, these electrocardiographic changes may be present in acute pulmonary embolism when no evidence of myocardial infarction is found at autopsy. When pulmonary embolism occurs in the presence of acute myocardial infarction, the electrocardiographic changes of acute cor pulmonale can be superimposed on those of acute myocardial infarction. Rheumatic fever patients, who fibrillate and have mitral stenosis, with evidence of right heart strain on their electrocardiograms, present a problem frequently in correct electrocardiographic appraisal. In such instances, one must be careful not to misinterpret these changes in the right precordial leads as due to pulmonary embolism.

In our series of cases electrocardiograms were taken in 41 instances. Sixty per cent of the electrocardiograms demonstrated evidence of pulmonary embolism. The pathognomonic pattern of acute cor pulmonale occurred in 37% of the patients, and nonspecific changes were observed in 23% of the cases. Nineteen electrocardiograms could not be

interpreted as showing evidence of pulmonary embolism. In most of these 19 cases, however, the electrocardiograms were not taken early enough nor often enough.

SUMMARY

In recent years various authors have stressed that pulmonary embolism is being underdiagnosed. We, too, are of this opinion and feel that the first prerequisite to increased diagnostic acumen is a high index of suspicion toward this complication. Particularly, we should be aware of the frequency of pulmonary embolism as a complication of congestive heart failure. Since it is desirable to diagnose pulmonary embolism on minimal findings, before a major attack occurs, we feel that the expression of apprehension, anxiety, and their concomitants should be considered "premonitory" symptoms of pulmonary embolism. These warning signs, often confirmed by early electrocardiographic studies, should lead to the institution of appropriate vigorous prophylactic treatment. In this regard, it is again emphasized that electrocardiograms should be obtained immediately and compared with control tracings. The electrocardiogram may be diagnostic or suggestive of pulmonary embolism when physical signs are absent. It is also conceivable that in the future, with improved techniques, a higher incidence of successful removal of an obstructing embolus from the main pulmonary artery or its branches may be accomplished.

CONCLUSIONS

1. Apprehension, anxiety, and related mental symptoms occur in a high incidence as a symptom "premonitory" to a major pulmonary embolus.

2. The electrocardiogram is a useful diagnostic tool to confirm the clinical impression of pulmonary embolization.

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Effects of Million Volt Irradiation on the Gastrointestinal Tract

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Previously there have been reported * certain aspects, comparatively short-term, of the effects of supervoltage irradiation on the normal gastrointestinal tract of young male adults, treated for testicular tumor. The present study is more inclusive and definitive in that autopsy findings, follow-up by correspondence, and thorough clinical examinations of approximately 100 patients, five years or more after completion of therapy, are available. In all, approximately 230 records more than five years after therapy have been evaluated.

A detailed history, including social, sexual, and economic adjustment after treatment, and physical examination, was made in the clinical study of each available patient. In all of these patients complete gastrointestinal x-rays were obtained. About 25 patients had cholecystograms. In many of the patients gastroscopy preceded by gastric biopsy, with use of a technique described by Palmer,[6] and sigmoidoscopy were performed. Determination of gastric acidity with a standard histamine dosage (0.5 cc.), liver-function tests (sulfobromophthalein [Bromsulfalein], cephalin flocculation, and alkaline phosphatase routinely, others occasionally), determinations of serum amylase, as well as complete blood study and urinalysis were routinely done for all patients. Other laboratory tests were performed when indicated on the basis of the history and physical findings.

It is quite obvious that the most accurate information would be obtained from those actually examined (96 patients) and the autopsied cases (72). In the living patients not examined (37) and those dead but without necropsy examination (29), the available records and follow-up correspondence permitted a rather accurate idea of their status. In the summary of irradiation effects to follow, we included the available information from all patients in the series. A presentation of some aspects of the data which are herein reported has recently appeared.[7] The inclusion of the patients treated with 200 kv. irradiation serve as a basis for comparison with the larger group treated with supervoltage (1000 kv.) therapy. In this paper, no specific data are given as to the number of days taken to complete therapy, since the majority of patients received therapy over an average period of 50 to 60 days. Not enough cases outside of the average range were encountered to make valid any conclusions relative to varying durations of therapy. The irradiation had been delivered to an area 10 cm. wide extending from the pubis to the xiphoid through anterior and posterior fields. The center of the area was in the midline for a tumor of the right testis, and 2 cm. to the left of the midline for a tumor of the left testis. In all cases, the antrum of the stomach, middle of the transverse colon, portion of the liver, and a segment of small intestine were irradiated.

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FINDINGS

Esophagus.—The method of treatment did not involve the area over the esophagus. Consequently no data were obtained in this series with reference to the effect of irradiation on the esophagus.

Stomach.—The effects of irradiation on the stomach are shown in Table 1. The dosage calculated to affect the lower third of the stomach was estimated at the level of the 11th dorsal vertebra. A word of explanation about the terms for degrees of injury is in order. Under "radiation dyspepsia" were included patients complaining of dyspepsia, indigestion, heartburn, belching, flatulence, and epigastric discomfort but in whom physical and roentgen examinations, as well as gastroscopy in some, did not reveal any abnormalities. In other words, there have been subjective upper gastrointestinal complaints since completion of therapy without objective findings. The research group well realized that at least some of these cases are functional in nature and felt that the term dyspepsia was adequate to indicate this possibility. Under the term "radiation gastritis" were included all cases which revealed abnormal x-ray changes of the stomach, such as mucosal thickening and narrowing of the antrum, without the demonstration of a definite ulcer. The other terms used in classifying degree of injury to the stomach are self-explanatory.

Clinically, patients who suffered injury to the stomach started complaining shortly after completion of therapy. The average case had symptoms of epigastric pain, belching, nausea, and, occasionally, vomiting two to three months after therapy. Perforation and hemorrhage when it occurred did so within six months of completion of therapy. Table 2, including only the examined and autopsied cases, reveals this graphically. In only a very few cases was the onset prolonged. In a previous paper [2] the findings at surgery were described. Following surgery, the patients were relieved of their gastric symptoms and did surprisingly well. The smallest dosage

TABLE 1.—*Summary of Effects of Irradiation on the Stomach*

Dosage Range at D11, r *	Total No. Irradiated		Radiation Dyspepsia		Radiation Gastritis		Radiation Ulcer		Ulcer with Perforation	
	1,000 Kv.	200 Kv.	1,000 Kv.	200 Kv.	1,000 Kv.	200 Kv.	1,000 Kv.	200 Kv.	1,000 Kv.	200 Kv.
Less than 1,000	..	4	..	..	..	..	..	..	..	..
1,000 to 1,499	3	7	..	..	..	..	..	..	..	..
1,500 to 1,999	10	13	..	..	..	..	..	1	..	..
2,000 to 2,499	7	20	..	2	..	..	1	..	..	..
2,500 to 2,999	4	14	1	1	..	..	..	..	..	..
3,000 to 3,499	11	3	1	..	..	..	1	..	..	..
3,500 to 3,999	13	2	1	..	2	..	..	..	..	..
4,000 to 4,499	19	4	..	..	5	..	..	..	..	..
4,500 to 4,999	27	..	1	..	5	..	3	..	3	..
5,000 to 5,499	34	..	..	..	8	..	6	..	4	..
5,500 to 5,999	14	..	..	..	7	..	2	..	1	..
6,000 and over	8	..	..	..	..	..	1	..	3	..
Total	150	67	4	3	27	0	14	1	11	0

* Dosage was estimated at the level of the 11th dorsal vertebra.

TABLE 2.—*Estimation of Onset of Symptoms in Stomach Lesions*

Radiation Damage	Living and Examined				Autopsy			
	Cases, No.	Months, No.			Cases, No.	Months, No.		
		Mean	Median	Range		Mean	Median	Range
Radiation dyspepsia.....	5	15	6	2-60	0	..	..	....
Radiation gastritis.....	16	4½	2	1-11	7	14	6	1-48
Radiation ulcer.....	5	19	5	1-72	5	4½	2	1-16
Ulcer with perforation.....	2	1	1	....	8	6½	4	1-30

which caused an ulcer was 2424 r. At the five-year follow-up examination in this patient, he was asymptomatic and no abnormalities were found. In some of the patients known to have had an ulcer previously, only a narrowed antrum by x-ray, in some with and in some without symptoms, was found at the five-year follow-up. We do not know whether the narrowing of the antrum is stationary or will progress to complete obstruction, but, after five years, such obstruction of this area has not yet been experienced in patients having previous ulceration due to radiation.

TABLE 3.—*Cases with No Effect on the Gastrointestinal Tract*

Dosage Range at L4, r	Cases, No. 1,000 Kv.	200 Kv.
Less than 1,000	..	3
1,000 to 1,499	1	6
1,500 to 1,999	6	5
2,000 to 2,499	9	10
2,500 to 2,999	..	11
3,000 to 3,499	6	16
3,500 to 3,999	7	4
4,000 to 4,499	9	4
4,500 to 4,999	6	..
5,000 to 5,499	8	1
5,500 to 5,999	12	..
6,000 and over	10	..
Total	74	60

In studies to be presented in detail elsewhere it has been found that irradiation over the antrum, even in large dosage, has no significant effect on the gastric secretion of acid after five years. The postulated mechanism of stimulation of gastric acidity by the antrum, removal of which at gastric resection for peptic ulcer most surgeons believe essential for a good result, is apparently not affected either shortly after (three years) or five years after considerable irradiation.

Table 3 indicates that 16 patients receiving between 3000 r and 4000 r and 36 patients receiving over 4000 r did not suffer any gastric effects. This indicates that some patients can tolerate high dosages, which give rise to gastric ulceration and perforation in other patients, without deleterious effect. In Table 1 it is noted that all but 3 of the 15 ulcers occurred in patients receiving 4500 r or

TABLE 4.—*Summary of Effects of Irradiation on the Intestines*

Dosage Range, r	Colon at L4 + 7%: Total No. Irradiated 1,000 Kv.	200 Kv.	Asymptomatic Constriction 1,000 Kv.	200 Kv.	Partial Obstruction 1,000 Kv.	200 Kv.	Perforation 1,000 Kv.	200 Kv.	Small Bowel at L4: Total No. Irradiated 1,000 Kv.	200 Kv.	Radiation Injury 1,000 Kv.	200 Kv.	Mesenteric Fibrosis at L4 1,000 Kv.	200 Kv.
Less than 1,000	..	4	..	..	..	..	..	..	..	4	..	..	..	..
1,000 to 1,499	1	4	..	..	..	..	..	..	1	5	..	..	..	..
1,500 to 1,999	7	4	..	..	..	..	..	..	8	5	..	..	..	..
2,000 to 2,499	8	9	..	..	..	..	..	..	10	12	..	..	..	..
2,500 to 2,999	3	9	..	..	..	..	..	..	1	14	..	1	..	..
3,000 to 3,499	5	19	..	..	..	1	..	..	7	17	..	1	..	1
3,500 to 3,999	6	13	..	..	..	..	..	..	9	6	..	..	..	..
4,000 to 4,499	11	4	1	..	1	..	..	..	13	4	2	..	..	1
4,500 to 4,999	9	1	..	..	1	..	..	..	14	..	5	..	1	..
5,000 to 5,499	20	1	1	..	1	..	..	..	20	1	7	..	1	..
5,500 to 5,999	23	..	1	..	3	..	..	..	31	..	5	..	2	..
6,000 and over	57	..	4	..	14	..	3	..	36	..	11	..	5	..
Total	150	68	7	0	20	1	3	0	150	68	30	2	9	1

more. All of the 11 patients with complications of ulceration had received more than 4500 r. On the basis of these observations it is our impression that the average patient can tolerate up to 4000 r of 1000 kv. therapy over the lower part of the stomach without danger and with little possibility of permanent gastric effects. Gastric changes occurring with less than 4000 r are more amenable to medical therapy, do not require surgery, and are not apt to leave residuals after five years.

Small Intestine.—Tables 4 and 5 present the data with reference to small bowel effects due to irradiation. Dosage over the area of the small intestine was calculated at the level of the fourth lumbar vertebra. The x-ray changes which were considered abnormal included segmentation, thickening of the mucosal pattern, and areas of constriction. Aside from the last roentgen finding, which occurred only in two of the examined patients after five years, the other findings were not considered specific enough to foretell with certainty the pathological changes in the small bowel. However, they were included in the light of clinical, surgical, and necropsy findings. In 20 cases perforation or obstruction due to fibrosis of the ileum or jejunum had occurred. Only three of these patients were living at the end of five years. Whether or not the x-ray findings listed above are significant in possibly detecting injury to the small bowel is questionable. The difficulty of evaluating such small bowel x-ray findings is well known. Table 5 indicates that there is a prolonged latent period from time of completion of irradiation to the onset of symptoms which usually betoken a catastrophe—either obstruction or perforation of the small bowel. Clinically, the patients are asymptomatic until this drastic damage has occurred. An accurate estimate of time of onset could be obtained only from the autopsied cases, which indicated that 12 to 24 months after treatment was the usual time that the difficulty began. A typical case was that of a 42-year-old veteran who had received 6266 r at L 4 in 61 days. He did well for 12 months, at which time he experienced sudden excruciating periumbilical pain. He was treated conservatively, and at necropsy perforation of the ileum with peritonitis was found. The rest of the gastrointestinal tract was not remarkable. In other cases, at necropsy, subacute perforation with matting of the mesentery, adhesions, and a more chronic type of peritonitis was seen. In some cases mesenteric fibrosis was demonstrated by x-ray findings of contraction of the small intestine with apparent limitation of mobility. Necropsy findings were confirmatory.

TABLE 5.—*Estimation of Onset of Symptoms in Intestinal Lesions*

Radiation Damage	Living and Examined				Autopsy			
	Cases, No.	Months, No.			Cases, No.	Months, No.		
		Mean	Median	Range		Mean	Median	Range
Colon lesions								
Asymptomatic constriction	4	?	?	60	3	35	48	3-54
Partial obstruction	6	19	16	2-48	9	17	12	4-30
Perforation	0	..	..	....	3	20	24	6-30
Small bowel injury	12	?	?	1-60	14	24	27	2-48
Mesenteric fibrosis	4	?	?	?	4	20	18	12-30

Table 4 illustrates that all of the small bowel injuries and mesenteric fibrosis occurred in patients receiving 4000 r or more of supervoltage therapy. Lesser amounts of 200 kv. therapy gave rise to three cases of injury in this category. It is our feeling that 4000 to 4500 r is a safe maximum dose of supervoltage therapy over the small intestine. One may wonder why more cases of radiation injury to the small intestine do not occur, since there is much more of it and its walls are thinner than those of the stomach and colon. It was the impression that the greater mobility of the small intestine prevented concentrated dosage of radiation in the same segment of intestine day after day.

It seems quite likely, in view of the prolonged latent asymptomatic period, that other cases of radiation injury, especially obstruction due to fibrosis, will be encountered in the future.

Colon.—An earlier study [4] has detailed the roentgen findings in this group. Tables 4 and 5 indicate the findings of colonic injury. Dosage to the colon was calculated at the level of the fourth lumbar vertebra plus 7%. The transverse colon bore the brunt of the dosage, owing to the position of the treatment portals, and most of the damage occurred in this area. Again the effects were delayed, as indicated in Table 5. On the average, perforation occurred 12 to 18 months after completion of therapy. Narrowing of the transverse colon, which was asymptomatic, was noted several times. The term "partial obstruction" is meant to indicate the presence of symptoms. In one case recently examined the patient had received 5890 r at L 4. Two years after completion of treatment onset of occasional perimbilical cramp-like pain was noted. A barium enema revealed a moderate constriction of the transverse colon. Five years after completion therapy there was marked constriction of the transverse colon but symptomatology was not severe. A year later a resection of this area was necessary because of complete obstruction.

It is our opinion that these colonic lesions are progressive and will eventually necessitate surgery in those patients in whom only mild changes are yet demonstrable by x-ray examination. Table 4 indicates that supervoltage therapy up to 4500 r seems safe as far as the colon is concerned.

Liver and Biliary Tree.—In nine cases which came to autopsy there was marked effect on the liver. The commonest finding was necrosis of the liver in the left lobe, since it was the part of the liver maximally exposed to radiation. In most of these cases, more than 5000 r was delivered to the area of the liver. In some cases these findings were noted within two months of completion of radiation, but other cases were not suspected until autopsy as long as two years after therapy. In three cases fibrosis was marked, and in the terminal clinical phase jaundice was noted in all of these cases. In one patient who survived more than three years after treatment, stricture of the common bile duct, in addition to generalized fibrosis of the liver, was found. In three of the autopsied cases fibrosis of the pancreas was noted. Over 5000 r was given in these cases. In none of the cases examined five

TABLE 6.—*Postmortem Findings in a Group Treated with 1,000 Kv. Therapy*

Case	Stomach Dose, D11, r	Small Bowel, L_4, r	Colon, $L_4 + 7\%$, r	Site of Radiation Damage
1	5,194	5,717	6,120	Small bowel, colon
2	6,456	6,456	6,908	Entire gastrointestinal tract
3	5,500	6,600	7,062	Stomach, liver
4	5,886	7,028	7,520	Small bowel, colon
5	5,350	6,300	6,740	Stomach, small bowel, colon
6	5,304	5,512	5,900	Stomach, colon
7	4,732	5,200	5,565	Stomach, small bowel, colon
8	5,750	6,750	7,220	Stomach, small bowel, colon, liver
9	4,536	5,376	5,752	Stomach, small bowel
10	3,888	4,176	4,470	Stomach, small bowel
11	6,048	6,500	6,955	Stomach, liver
12	4,400	5,290	5,660	Stomach, colon
13	5,500	6,100	6,530	Stomach, small bowel, colon, liver
14	5,280	5,950	6,370	Stomach, small bowel, colon, liver
15	4,800	5,568	5,960	Stomach, small bowel, colon
16	5,000	5,500	5,885	Stomach, liver
17	5,779	6,226	6,662	Stomach, small bowel
18	5,400	5,400	5,778	Entire gastrointestinal tract
19	6,100	6,100	6,530	Stomach, small bowel, colon
20	5,940	6,210	6,645	Stomach, small bowel, colon
21	5,100	6,032	6,454	Stomach, small bowel, colon
22	5,000	5,880	6,292	Stomach, small bowel
23	5,300	5,860	6,270	Stomach, small bowel

years after completion of irradiation was there evidence of hepatic, pancreatic, or biliary-tree abnormality.

Combined Gastrointestinal Lesions.—It was to be anticipated that in some of the patients who received large doses of irradiation more than one organ in the gastrointestinal tract would be affected. Table 6 shows the findings of 23 autopsied cases in this respect. It will be noted that in practically all of these cases 5000 r or more of supervoltage irradiation was given. The findings in Table 3, wherein it was shown that 30 patients received 5000 r or more without any adverse effect on the gastrointestinal tract as long as five years after treatment, are in vivid contrast to the findings in Table 6. They serve to emphasize the marked variation and unpredictability in apparent sensitivity of the gastrointestinal tract in different persons to the effects of supervoltage therapy.

SUMMARY

A review of the effect of 1000 kv. irradiation on the normal gastrointestinal tract of young male adults, 96 of whom were clinically studied five years after completion of irradiation, has been presented, with an estimation of the tolerance dosage to such radiation.

All parts of the gastrointestinal tract were affected, but the sensitivity varied in the individual patient markedly. It is also shown that the same dosage of irradiation causing damage to the gastrointestinal tract in one person can be tolerated by another patient without any damage.

Onset of symptomatology occurred earliest in cases in which the stomach was injured. Radiation injury to the small intestine and colon resulted in a more subtle clinical picture, with a delay in onset of symptoms for many months and even years after completion of therapy.

On the basis of these observations, a safe maximum tolerance dose to the antrum of the stomach would appear to be 4000 r delivered in 50 to 60 days.

The maximum tolerance dose to small intestine is in the range of 4000 to 4500 r, while the large intestine can safely be exposed to 4500 r.

The biliary tree and liver appear to be affected by a dose of 5000 r or more.

Study of cases five years after therapy indicates that the incidence, extent, and nature of the radiation injury to the gastrointestinal tract may not yet have been fully catalogued.

Cancer of the gastrointestinal tract has not been encountered in this study.

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The Peptic Ulcer Personality

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It has become common in the last few years for doctors and the laity to refer to certain persons as being of the ulcer type. A number of articles and even a book have been written describing the ulcer personality. Yet we could not feel certain that the ulcer patients we saw belonged to a definite personality type and we found that others had also raised questions. Ivy,[84] for instance, stated "In reading in the psychosomatic literature I have been impressed with the rather wide range of personality type which have been described as 'typical' of the patients with peptic ulcer, as well as the absence of a control group." We, therefore, reviewed the literature on the subject to determine whether the methods used in studying the problem seemed reliable and whether the investigators agreed on one specific ulcer personality.

TECHNIQUES USED IN STUDY OF THE ULCER PERSONALITY

Articles that discussed the ulcer personality were first examined to determine what method of study the author used. It was found that in half of the articles no method of study was described. This was true not only of summary articles that briefly discussed the ulcer personality along with other subjects but also of articles that were entirely devoted to a description of the ulcer personality. The basis for these descriptions, it must be assumed, was the authors' clinical impression. The remaining articles, in which the technique of study was described, could be divided into three groups on the basis of the three general methods used: (1) interview, (2) psychoanalysis, and (3) psychological testing.

Pertinent facts about the technique used in these studies have been reviewed in Tables 1, 2, and 3. The following defects in technique were found frequently in these studies:

No distinction was made between patients with gastric ulcer and patients with duodenal ulcer. As the two kinds of ulcer do show differences clinically, a difference in the associated personality would seem possible. Wretmark,[1] who studied the personality of patients with duodenal and gastric ulcer separately, found that there was a difference. The gastric ulcer patients had no specific personality pattern that distinguished them from controls, whereas the duodenal ulcer patients did have a specific personality pattern. Hamilton[11] found that duodenal ulcer patients showed greater evidence of anxiety neurosis than gastric ulcer patients.

No distinction was made between male and female ulcer patients. Yet, just as there is a different incidence of ulcer in men than women, there might be a different ulcer personality. Those who studied them separately found that there were differences in personality. The female patients were more emotionally unstable,[4] more frequently psychoneurotic,[18] and more likely to make a poor adjustment to their environment.[15]

Conclusions about the ulcer personality in the general population have been drawn from studies of samples that were not representative. Kapp and co-workers,[16] who

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TABLE 1.—*Interview Studies*

Author	Sex			Site			Type of Patient	Control or Comparison Group	Method of Study	Approximate Time Spent with Each Patient
	M	F	Not Stated	Duodenum	Stomach	Not Stated				
Wretmark	292	...	...	226	66	...	Swedish, all economic levels	Person in same town, born after each respective patient	Detailed personal interview and questionnaire	.....
Ruesch and co-workers	64	...	...	64	...	...	42 navy enlisted men, 22 civilians	Patients with delayed recovery from an illness	Focused interviews and psychological test	8-10 hr.
Draper and McGraw	15	6	...	...	21	...	General hospital	12 patients with gall-bladder disease	Structured interview and information from ward nurse and social workers	2-3 hr.
Davies and Wilson	75	25	...	...	...	100	Lower class	Hernia patients of same age and class	Interviews scored for fears, anxieties, needless activities, and mood swings	.....
Mittleman and Wolff	27	3	...	25	5	...	.....	13 normal subjects with no gastrointestinal complaints	Interviews to ascertain predominant emotions and other personality features, record gastric motility and secretion during stress interview	.....
Finesinger	...	...	59	...	...	59	Clinic	Patients with fatigue or atopic dermatitis, also healthy sailors and pilots	Interview and questionnaire	.....
Klein	...	...	20	...	...	20	Clinic	80 other patients with G. I. complaints	Interview and psychological tests	.....
Hamilton	100	...	...	50	50	...	Clinic	50 nonulcer dyspeptics, 50 "controls"	Interview for objective data and questionnaire filled by patient	.....
Grace and Graham	...	...	9	9	...	...	Clinic	Urticaria 31, eczema 27, cold hands 10, asthma 7, etc.	Interview to elicit attitude toward situation associated with attack	10 or more hours
Montgomery and co-workers	23	...	...	23	...	...	Sailors and Marines	22 patients with upper G. I. complaints	Interview to determine presence of psychoneurosis	.....
Schildkrout	97	...	...	87	...	...	Army hospital	Functional dyspepsia 21, gastroduodenitis 61, psychoneurosis 18	Interview for possible psychoneurosis or psychosis	.....
Kezur and co-workers	...	25	...	...	...	25	Mostly clinic	None	Psychiatric interview and data from relatives, psychologists, and social agencies	3-300 hr.
Kapp and co-workers	20	...	...	...	...	20	Clinic	None	Psychiatric interview and data from relatives and friends	3-8 hr.
Gaskill	46	22	...	...	...	68	Clinic	None	Psychiatric interview	5-10 interviews
Gainsborough and Slater	130	32	...	117	45	...	London clinic	None	Psychiatric interview	.....
Winkelstein and Rothschild	33	...	...	33	..	...	Gastrointestinal clinic	None	Psychiatric interview	.....
Halsted and Weinberg	100	...	...	...	...	100	Enlisted men in hospital, North Africa	None	Interview to evaluate nervous and emotional factors in personality	2 hr.
Wilson	...	...	50	...	...	50	.....	None	Superficial biographical interviews	.....
Moses	25	...	...	25	...	...	Naval inductees	None	Interview	2 hr.
Tschering	+	...	...	...	+	...	Berlin clinic	None	Interview	.....
Rubin and Bowman	100	...	100	...	...	...	Marginal economic	None	Interview	½ hr.

TABLE 2.—*Psychoanalytic Studies*

Author	Date	Sex			Site of Ulcer			Type of Patient	Analysis Completed at Time of Publication	Length of Study
		M	F	Not Stated	Duodenum	Stomach	Not Stated			
Alexander	1934	..	..	6	..	..	6	.....	.....	.....
Bacon	1934	..	2	..	2	..	..	Successful professional woman, business woman,	One, not Other, ?	One, 6 wk. Other, ?
Levey	1934	1	.	..	1	..	..	Technology student	.....	10 wk.
Van der Heide	1940	2	..	..	..	1	1	Salesman, industrial director	One, not Other, ?	.....
Stone	1947	1	..	..	1	..	..	Real estate broker	Yes	776 hr.
Alexander	1947	1	..	..	1	..	..	University student	Yes, short type	36 sessions (10 mo.)
Pickford	1948	1	..	..	1	..	..	Wage clerk England	No	7 interviews
Garma	1950	6	..	..	..	..	6	Upper class, Argentina	.....	.....

TABLE 3.—*Psychological Test Studies*

Author	Test	Sex			Site of Ulcer			Type of Patient	Control or Comparison Group
		M	F	Not Stated	Duodenum	Stomach	Not Stated		
Hackfield	Rorschach	..	..	6	6	..	..	.....	8 Graves disease, 7 hypertension, etc.
Ruesch and co-workers	Rorschach, Minnesota Multiphasic, Wechsler-Bellevue	59	..	..	59	..	..	42 Navy enlisted men, 17 civilians	Patients with delayed recovery
Kaldegg and O'Neill	Rorschach	16	4	..	20	..	..	Ward patients, England	.....
Brown and co-workers	Rorschach	25	..	..	25	..	..	Veterans Hospital	25 veterans with other complaints
Marquis and co-workers	Rorschach, Otis SA, TAT, Gamin, Draw-a-Person	16	..	..	..	..	16	Age, 25 to 56; Ed. 6th grade to college	13 similar people with another psychosomatic complaint
Modell and Potter	Draw-a-Person	9	2	..	..	..	11	Ward patients	10 hypertension, 10 asthma
Hecht	Level of aspiration	30	..	..	..	..	30	Veterans Hospital	30 ulcerative colitis
Blum and Kaufman	Blacky pictures	..	..	14	..	..	14	.....	30 normal, 30 paranoid schizophrenia, 30 schizophrenia

studied a charity hospital group, called attention to this possible source of error because of their experience: The only patients in their group who were ambitious and successful, the traditional ulcer type, had been admitted to that hospital because of an emergency. If it had not been for these emergency admissions they might have concluded that the ambitious, successful type did not get ulcers. On the other hand, the specialist, who saw only the successful business and professional men who could afford his fee, could have formed his impression, that all ulcer patients were ambitious and successful, because of the particular class of patients whom he saw.

The evaluation of personality traits is difficult. An investigator usually has to spend several hours observing and interviewing the patient in order to form a

reasonably accurate picture of his personality. The patient's description of himself, as obtained through direct questioning or a questionnaire, may well be inaccurate, for it may vary with his mood or his reaction to the interviewer. Yet in several reports the patient's summation of himself was used as the basis for describing an ulcer personality. Only a few authors indicated that they had spent several hours studying their patients. A few others specified that they obtained additional information about the patient from his friends and family or from those who observed him on the ward.

None of the interview studies would be judged by present standards to have been adequately controlled. In only 11 of the 21 was there any control or comparison group used at all. In not one of these 11 did the author describe a specific technique that he had used to prevent the interviewer from knowing which patient had ulcer and which did not. The interviewer's unconscious bias, therefore, could have influenced his findings in all of these studies. The psychoanalytic studies do not describe any examination of controls for the mechanisms found in peptic ulcer patients. In some of the studies based on psychological testing, controls were tested as well as ulcer patients. In only one of these studies,[38] however, it is stated that the findings were analyzed without the observer's knowing which patients had ulcer and which did not.

The significance of the observations made by psychoanalysis is limited because the number of patients studied is so small, 20 in all. Further, a number of these 20 patients did not complete their analysis. In fact, only two cases are specifically reported to have completed their analysis, and one of these two had only a short analysis, 10 weeks. Several of the other cases are specifically noted not to have completed their analysis.

The number of patients studied by any psychological test other than the Rorschach has also been small, and several of the groups studied by the Rorschach test itself were small. One study [38] covered 12 patients, but these were actually divided into two groups of 6 patients each; and conclusions about two types of ulcer personality were drawn from these two samples.

TABLE 4.—*Incidence of Psychoneurosis in Peptic Ulcer Patients According to Various Authors*

Author	Sex			Site of Ulcer			Per Cent of Patients Found to Have Psychoneurosis
	Male	Female	Not Stated	Duodenum	Stomach	Not Stated	
Friedman	46	..	..	..	..	46	2
Halsted and Weinberg	100	..	..	..	..	100	5
Kirk	200	.	..	200	..	..	10
Schildkrout	10	.	..	..	10	..	10
Sullivan	..	..	..	..	..	..	11
Gainsborough and Slater	130	..	..	97	33	..	15
Gainsborough and Slater	32	..	..	20	12	..	19
Schildkrout	87	.	..	87	..	..	23
Flood	47	..	..	47	..	..	53
Finesinger	..	..	59	..	..	59	60
Davies and Wilson	75	..	..	..	..	75	76
Davies and Wilson	..	25	.	.	..	25	84
Cox and Junilla	161	..	.	..	..	161	100
Kezur	..	25	..	25	..	..	100

Usually the author did not report how often he found a given characteristic, such as ambition, in his patients. Only rarely did he analyze his findings for statistical significance. Generally he reported his conclusions, not his data.

NATURE OF THE ULCER PERSONALITY

After a review of the techniques used in the study of the ulcer personality, the next

problem was to determine whether there was any agreement on the nature of this personality. The descriptions given by different authors were examined for their answers to three questions:

1. Is the ulcer patient usually a psychoneurotic?

2. What are the characteristics or traits of the ulcer personality?

3. What are the psychodynamics of the ulcer personality?

The incidence with which various authors found psychoneurosis in their ulcer patients is indicated in Table 4. It is clear that there is no agreement. There was also no agreement among authors who made general statements on the subject but did not give definite figures of incidence and hence were not listed in the Table: Jones [53] and Robinson * both stated that ulcer patients were not psychoneurotic whereas Cathcart [65] stated that ulcer patients frequently showed frank anxiety neurosis, and Hamilton [11] found that duodenal ulcer patients definitely showed signs of anxiety neurosis more frequently than controls. There did seem to be some agreement among those who described psychoneurosis in that the type found was usually anxiety neurosis.

The various authors also did not agree on the traits or characteristics that distinguished the ulcer personality. Thirteen denied that there was any characteristic ulcer personality.† Others stated that there were distinctive personality traits, but these authors differed amongst themselves; traits mentioned by some were not mentioned or were even contradicted by others (Table 5). Three traits, however, were frequently described, although none of them was described by as many as a third of the authors: drive, conscientiousness, anxiety. There was disagreement as to whether the drive was sustained or intermittent. There was also disagreement as to whether the anxiety was overt or covert. Some authors stated that their patients appeared obviously anxious. Others stated that their patients appeared calm but when questioned would indicate that they felt restless or impatient. One author noted that his patients appeared calm during the interview but restless on the ward. Finally a number of authors did not indicate whether they were describing overt or covert anxiety.

Although other traits were described, the statements about most of them were contradictory. Thus, the comments that the ulcer patients were intelligent contrasted with reports that they showed average scores on AGCT and IQ tests. Similarly, the comments about the ulcer patient's heterosexual adjustment were all different:

Good heterosexual adjustment [54]

Sex problems in only 1 of 32 male patients, but many led undersexed life [18]

Sexual life normal but adult sexual activities have never meant much to him, and conflicts over masturbation more severe than with others [21]

Sexual conflict, mild or moderate, in 18% of patients [20]

None with a satisfactory sexual adjustment (women) [15]

Almost without exception there are strong signs of severe sexual maladjustment [38]

Obvious sexual disturbances in 5 of 10 patients [39]

Sexually constricted, with concern about conventional behavior [23]

A number of authors, particularly the psychoanalysts, discussed the psychodynamics of the ulcer patient. They suggested that the ulcer patient had a specific type of conflict. These authors differed among themselves in two ways. First, they did not agree on the nature of the conflict. Second, they did not agree on whether the conflict was or was not associated with a specific personality type.

There were a variety of psychodynamic patterns or conflicts described, but many of the American authors described essentially the same conflict, although they did so in somewhat different terms. This conflict was first reported by Alexander, in 1934: The ulcer patient has a strong desire to be loved and taken care of (others have referred to this as the wish to be dependent

* References 74 and 75.

† References 7, 10, 15, 16, 25, 26, 36, 56, 59, 66, 67, 83, and 84; Jordan, S. M., in discussion on Ivy [83]; Cobb, S. F., in discussion on Ivy.[83]

or passive). In most cases he rejects this desire because it is incompatible with his ego's desire for independence and activity. In a few cases he expresses his passive wishes openly but is thwarted by circumstances in his environment. When this wish to receive or be loved is thwarted, by either the patient's ego or the environment, it becomes converted along regressive pathways into the wish to be fed, which in turn leads to chronic stimulation of gastric function.‡

Some authors who described this conflict, like Alexander, did not recognize a specific ulcer personality. Others did recognize an ulcer personality and explained the ambition and drive that they observed as the patient's reaction to passive wishes that his ego could not tolerate. Still others § described two types of patients and stated that these patients differed because of the way in which they handled their passive wishes: one group was openly passive; the second attempted to compensate for their passivity and therefore appeared ambitious and aggressive.

Other psychodynamic patterns were described:

> Duodenal ulcer occurred when something happened and the patient was seeking revenge, wanted to injure the person or thing that had injured him.[12]
>
> Familial stresses of every-day life were having a more than normally large effect on the vegetative nervous system of constitutionally susceptible persons.[18]
>
> All of 33 patients had a subacute or chronic conflict of a typical kind, i. e., nothing could be done about it except to bear it to the best of one's ability.[19]
>
> Ulcer patients possessed abnormally high needs for security.
>
> Conflicts activating fear of insecurity lead to hematemesis.[21]
>
> Ulcer patients are aggressive obsessionals with certain oral tensions, in whom sublimations have failed in a special way which we do not clearly understand, so that under stress there is a regression to infantile aggressiveness directed to the gastrointestinal tract.‖
>
> There exists in the ulcer patient's unconscious psychic images of an internalized mother, that harm him precisely in his digestive tract because, as a consequence of his conflicts, he has regressed partially from genital to oral-digestive conduct.¶
>
> Chronic anxiety may cause increased acid secretion and ulcer.#
>
> Hostility or anger may be responsible for increased acid secretion and ulcer.[44]
>
> A man is encountering obstacles that prove to him a trial and a handicap which he must because of his nature endeavor to overcome.[46]
>
> Ulcer is due to a conflict situation in which the patient feels compelled to perform in a certain manner but fears that he cannot.[66]

Some of the studies using psychological tests and miscellaneous techniques have yielded results comparable to those found by interview and psychoanalysis. A level of aspiration test [40] showed that ulcer patients had more drive than the ulcerative colitis patients used as controls. Responses to the Blacky Picture Test [41] brought out evidence for two types of ulcer patient: a primary or openly passive and a reactive or independent type. This same dichotomy was observed by another investigator who used a battery of psychological tests.[38] The results of a human figure drawing test [39] of 10 ulcer patients showed evidence of their need for security and conformity as well as their resentment.

Electroencephalograms * showed a high alpha index, a sign according to Saul, Davis, and Davis,† of passivity.

Gastric acidity was found to be increased when patients were anxious ‡ or hostile,[44] evidence that these were important reactions in ulcer patients.

The Rorschach findings reported by different investigators were not consistent. The scores on certain specific responses did show some similarity; but the investigators' inter-

‡ References 2-5, 7-9, 15, 16, 21, 23-30, 37-39, 41, and 64; Finesinger, J. E., in discussion on Ivy.[83]

§ References 8, 9, 16, 24-26, 38, and 41; Finesinger, J. E., in discussion on Ivy.[83]

‖ References 31 and 32.

¶ References 33 and 34.

References 42 and 43.

* References 23 and 24.

† References 85 and 86.

‡ References 42 and 43.

TABLE 5.—*Personality Traits of Peptic Ulcer Patients According to Various Authors*

Traits	Number of Authors Describing the Trait	References	Opposite Traits	Number of Authors Describing the Trait	References
Drive	11	6, 20, 45, 47, 48, 53, 54, 58, 63, 74, 75, 79, 81	.....	..	.....
Ambitious	4	8, 9, 21, 40, 47, 48, and Finesinger, in Ivy [83]	.....	..	.....
Dynamic	1	61	.....	..	.....
Overactive	2	3-5 and 50	Slow-moving	1	52
Energetic	3	18, 69, and 71	.....	..	.....
Hard worker	2	7 and 23	Less able to work hard	1	11
Persistent	4	7, 23, 39, and 71	Activity not sustained	4	16, 54, 74, and 75
Conscientious	7	3-5, 23, 54, 61, 63, 66, and 71	.....	..	.....
Meticulous	4	1, 8, 9, 66, 74, 75, and Finesinger, in Ivy [83]	Slovenly	1	52
Perfectionistic	1	53	.....	..	.....
Obsessive	3	18, 21, 58	Not obsessive	2	2 and 61
Compulsive	2	1 and 6	Not compulsive	2	2 and 61
Anxious	14	1, 8, 9, 11, 18, 35, 36, 49, 50, 51, 54, 63, 65, and Finesinger, in Ivy [83]	.....	..	.....
Nervous	3	1, 3-5, and 70	Not complain of anxiety	1	7
Tense	4	6, 53, 58, and 71	No evident anxiety	1	20
High strung	4	47, 48, 69, 70, and 72	.....	..	.....
Emotional	3	3, 4, 5, 69, and 72	Affectively indifferent	1	1
Emotional instability	3	36, 37, and 49	Calm exterior	5	7, 20, 65, 74, 75 and 79
Resentful	4	8, 9, 39, 65, 79, and Finesinger, in Ivy [83]	Suppress emotions except anger	1	21
Hostile	5	7-9, 17, 20, 44, and Finesinger, in Ivy [83]	Unable to get outwardly angry	1	19
Introverted	3	1, 22, and 49	Extraverted	1	3-5
Find friendship difficult	1	21	Friendly	1	54
Aggressive	3	7, 20, 61	Unaggressive	1	63
Challenging disposition	1	74 and 75	Timid	2	16
			Unobtrusive	1	52
Intelligent	5	3-5, 36, 74, 75, 81, and 82	Average IQ	1	2
			Average AGCT	1	77
			Low intelligence	1	52
			Mathematical ability poor	2	3-5, 74, and 75
Successful	3	5,40,47	Poor executive	1	3-5
Executive ability	2	41, 68	Reliable subordinate	1	63
Worry	6	4, 18, 40, 47, 67, 68	Apparent indifference to symptoms	4	20, 53, 74, 75 and 82
Alert	5	40, 41, 63, 72, 74	.....	..	.....
High-principled	1	40	Exploit their defect	1	52
Overly honest	1	54	.....	..	.....
Patriotic	1	72	Not try to adjust to Army	1	51
Keen sense of humor	1	3	.....	..	.....

pretations of the test results as a whole were different (Table 6).

COMMENT

There have been many improvements in technique since the first articles gave impetus to the study of the personality of peptic ulcer patients. Investigators have found that men and women should be studied separately,§ as should gastric and duodenal ulcer patients.‖ Generalizations about all ulcer patients should not be drawn from studies of a special social class.[16] Controls should be used, and they should differ from the patients only in that they do not have ulcers.[1] As this was not fully appreciated in the past, reports were often made after less than an hour's study. We also recognize the importance of statistical analysis to determine the significance of findings.[11] This type of analysis had been used in only a few of the studies reviewed.

A satisfactory method for using controls also has to be developed. In determining the effect of a drug,[87] it has been found that the investigator must not only examine controls who were given a placebo but must also not know himself which patients received a placebo and which the drug. Otherwise, his unconscious bias may lead him to find the effect that he expected from the drug. Controls were used in only a few of the studies of the ulcer personality, and the investigator knew whether he was examining an ulcer patient or a control in all but one of them. In this study,[38] psychological tests were administered to ulcer patients and controls. The results were then given to another examiner to analyze "blind," i. e., without knowledge of the test subjects' diagnosis. Interview studies presented a different problem, because an interviewer usually inadvertently learned enough about the patient's symptoms and treatment to make the diagnosis. This problem was not solved in these studies. Yet until it is solved interview stud-

TABLE 6.—*Rorschach Scores Obtained in Various Studies of Ulcer Patients*

Author	Patients, No.	Movement: Color (M:C)	Animal Movement: Human Movement (FM:M)	Small No. of Responses (Low R)	Whole Responses: Detail Responses (W:D)	Color Form: Form Color (CF:FC)	Interpretation
Hackfield	6	+	..	..	−	..	Sensitive, selfconscious disposition, chronic anxiety and fear states
Ruesch and co-workers.	59	+	+	+	+	+	Primitive simple personality development without mature ego
Kaldegg and O'Neill.'	20	−	+	+	+	+	No predominance of a single personality type
Brown and co-workers	25	−	+	+	±	+	Deal with their environment at an impulsive, emotionally immature level
Marquis and co-workers							
Primary	6	..	−	..	..	+	Oral preoccupation and fixation, regressive trends, sexual maladjustment and depressive signs
Reactive	6	..	+	..	..	−	

Failure to recognize these points in earlier studies led to errors that can now be avoided.

An entirely satisfactory method for evaluating personality, however, has still not been developed. With the methods we now have we can obtain valuable information, but it is not as reliable or precise as the data we can obtain about more tangible phenomena. We do realize that an investigator must spend a minimum of several hours interviewing and observing a patient before he can draw any reasonably valid conclusions about the patient's personality.¶

§ References 3-5, 7, and 18.

‖ References 1 and 11.

¶ References 2 and 12.

ies cannot be trusted. A possible solution might be to take tape recordings of interviews, delete the information suggesting the diagnosis, and then present the abbreviated recording to another psychiatrist for analysis.

A number of different personalities were described as the typical ulcer personality in these studies. There was no whole personality or feature of personality that was agreed upon by as many as a third of the investigators. The following features, however, were mentioned frequently: First, the conflict over passivity; second, the presence of the traits of drive, meticulousness, and anxiety.

We cannot say whether the fact that a number of investigators described the same personality features is significant; for this may be due to a defect in their technique. Undoubtedly most investigators had reviewed prior studies and had some expectation of what they might find. Yet, as previously noted, they did not take adequate precautions to prevent this from influencing what they did find. Thus, psychiatrists, who did many of these studies, were acquainted with the pioneer work of Alexander [25] and might have been influenced by it. The following suggests that they actually were: The psychiatrists who psychoanalyzed 12 of the 20 reported cases had worked in Alexander's clinic.# They all found the conflict described by Alexander. A psychiatrist from England * and one from Argentina † together psychoanalyzed seven of the remaining eight cases. They did not find the conflict described by Alexander.

Alexander himself pointed out that the active-passive conflict was seen not only in ulcer patients. Three of the nine patients on whom he based his original description of the conflict had gastric neurosis. He indicated that he had also seen the conflict in persons who had no gastrointestinal disease. This observation of Alexander's calls for further investigation. We must know how often this conflict can be found in the general population before we can decide how significant is the fact that it is found in ulcer patients.

The improvements in technique that have developed out of these studies of the ulcer personality have two effects. They make possible more reliable investigations in the future, but they also raise questions concerning the reliability of investigations done in the past. Therefore, the nature or even the existence of the ulcer personality cannot be considered established.

SUMMARY

The techniques used in past studies of the ulcer personality would not be acceptable by present standards.

Investigators do not agree on the nature or even the existence of a specific ulcer personality.

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Adenomatous Goiters and the Serum Precipitable Iodine

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In this communication we intend to describe our experiences with the use of the level of the serum precipitable iodine (SPI) as a laboratory aid in appraising whether a patient with an adenomatous goiter is euthyroid or hyperthyroid. No cases of Graves' disease (exophthalmic goiter) are included. The distinction between the adenomatous goiter and the hyperplastic goiter of Graves' disease appears to be a valid distinction, clinically, pathologically, and possibly etiologically.* Therefore, since we do not consider "hyperthyroidism" to be a single entity, it seems appropriate that this diagnostic technique (the SPI) be evaluated in a single category; namely, the adenomatous goiter.

Many diagnostic difficulties arise in the evaluation of the total functional state of the adenomatous goiter, particularly if the goiter has been present for many years, if other diseases complicate the clinical picture, and if the signs and symptoms of hyperthyroidism are not definite. We frankly confess that not infrequently, in spite of making every effort to appraise the patient by a careful history and physical examination, we have been forced to conclude our initial impression with such dubious remarks as the following: "The patient is probably euthyroid but could be mildly hyperthyroid." In these situations feelings of omniscience quickly vanish. When time-honored supplementary laboratory aids fail us (e. g., the basal metabolic rate), the only certain method for final evaluation is careful observation, with time, of the patient's response to treatment of associated diseases, his response to antithyroid drugs or thyroidectomy, and repeated examinations.

The difficulties inherent in the use of the radioiodine-accumulating function of the thyroid in the evaluation of the functional state of the adenomatous goiter have already been noted by Keating and his associates.[4] Our studies do not include this diagnostic technique.

MATERIALS AND METHODS

The records of 90 patients with adenomatous goiters who had SPI determinations were carefully reviewed. These patients were admitted to the hospital over a 27-month period, and all were observed by two or more members of the metabolic service. They consisted of 81 women, whose ages ranged from 33 to 82 years, and 9 men, whose ages ranged from 56 to 79 years (mean age for entire group was 64.1 years). The majority were hospitalized for conditions other than thyroid disease (e. g., heart failure, pulmonary emphysema, or anemia), and the finding of an adenomatous goiter was usually considered to be a secondary, though not necessarily an unimportant, finding. No patient was included in this study who had had iodides administered in such form or at such time as to complicate the SPI.

The patient's clinical findings were first evaluated by the general medical section and then carefully reevaluated by a metabolic service. In all cases a definite clinical impression was made prior to employment of any laboratory aid, i. e., whether the patient was thought to be definitely euthyroid or definitely hyperthyroid or whether he could not be categorized securely in either group at the time

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* References 1-3.

of the initial examination. The SPI was determined at least once, and frequently twice, for all 90 patients; the serum cholesterol level was determined for 44, but satisfactory basal metabolic rates were obtained for only 18. The latter unfortunate fact was due in large part to the fact that most of our patients had complicating diseases, that the mean age of our patients was 64.1 years, and occasionally, but rarely, we believe, to our own negligence in obtaining this test. In any event, the basal metabolic rate was merely considered to be a part of the problem involved in the final appraisal of the patient; in no instance was a patient placed in a particular group on the basis of this test only.

After a careful review of the records of the 90 patients, they were categorized into three groups: (1) those clinically, and seemingly unequivocally, euthyroid with a normal SPI, (2) those clinically hyperthyroid with an elevated SPI, and (3) those who presented a real problem in diagnosis, i. e., those who presented a doubtful clinical picture or who were thought initially to be euthyroid but whose SPI was elevated above our normal range (7.0γ per 100 cc.). The analysis and criteria for final evaluation in these three groups are presented below. In other words, we went to the patient first, then to the laboratory, and lastly back to the patient and his record for final appraisal. The SPI per se, like the B. M. R. and other tests, did not influence the ultimate diagnosis; the response to treatments and follow-up studies provided the basis for final classification.

Previously, one of us (W. W. E.) determined the SPI level of 117 persons without thyroid disease.[5] A few of these were healthy employees, although the majority were hospitalized patients who were not critically ill and represented a good cross-section of the hospital population. In this control series 91.5% had an SPI between 3.5γ and 7.0γ per 100 ml. of blood (mean, 5.1γ). For convenience, and because the distribution curve is slightly skewed, this is considered to be our "normal" range. Only 4.25% had a level over 7.0γ, and none had a level over 8.0γ. The SPI was determined by the digestion-distillation technique as modified by Danowski and associates.[6] All determinations were carried out in duplicate on 3 ml. aliquots of serum. In our hands duplicate determinations almost always check within 0.5γ; if not, a third determination is made.

RESULTS

Those Clinically Euthyroid and Having a Normal SPI

In 52 (58%) of the 90 patients, a definite clinical impression of euthyroidism (initially and with extended subsequent examinations) was made and an SPI below 7.0γ was observed. The range varied from 2.5γ to 6.9γ per 100 ml. The mean was 5.0γ, which is almost identical with our control mean of 5.1γ for patients without thyroid disease.

Four patients (4.4%) had levels below 3.5γ; 4.2% of our controls had SPI below this concentration. Three of the four patients were women, aged 52, 54, and 62 years, with arteriosclerotic heart disease, and one was a man, age 74 years, with pulmonary disease of undetermined type, probably bronchogenic carcinoma. The values were 2.5γ, 2.7γ, 3.3γ, and 3.3γ per 100 ml. None of these had clinical evidences of myxedema. An occasional value below 3.5γ would be expected.

Ideally, from the standpoint of clinical investigation, it might be assumed that all of these patients should have been given a thorough trial of antithyroid drugs or should have had a thyroidectomy before it could be finally concluded that all were definitely euthyroid. However, in none of these patients was there any clinical suspicion that they were possibly hyperthyroid at the time of initial examination. If so, they would have been placed in the "problem" group. Further, the hospital and outpatient records of these 52 patients were carefully reviewed, and there was nothing in their subsequent course (response to treatment of associated conditions, symptoms, or physical findings) which made us feel they were not euthyroid. All 52 patients were observed for at least several weeks in the hospital, and in most cases the observation period extended over many months, either in the hospital or in the outpatient departments, or during readmissions to the hospital. Satisfactory basal metabolic rates were obtained in six patients, and these were normal. A subtotal thyroidectomy was performed in seven patients, and, except for the development of postoperative myxedema in one, no change in their status occurred.

While we did our best to exclude the possibility, it is still possible that an occasional patient in this group was, in truth, mildly hyperthyroid. It was not feasible, nor did we desire to perform subtotal thyroidectomies on all of

these patients. Further, we could see little justification to administer antithyroid drugs to persons who appeared to be clinically euthyroid in every respect. In general, in such situations, it would be as difficult to evaluate the effects of surgery or medical therapy as it would be to evaluate the patients without such "therapies"; the final conclusion would be equally elusive for either situation. Thus, while this aspect of our studies has this particular weakness, we feel that the occurrence of mild hyperthyroidism in this group was rare.

Those Clinically Hyperthyroid and Having an Elevated SPI

In 10 patients an unequivocal clinical impression of hyperthyroidism was made at initial examination. There was no hesitation to proceed with measures to control the rather obvious hyperthyroid state. In 3 of the 10 a subtotal thyroidectomy resulted in alleviation of the symptoms and signs of hyperthyroidism, and in the remaining 7 patients the administration of propylthiouracil (300 mg. per day to one, 450 mg. per day to five, and 600 mg. per day to one) also caused regression or complete disappearance of the manifestations of hyperthyroidism. The SPI values for these 10 patients were as follows: 7.3γ, 7.6γ, 7.7γ, 8.1γ, 8.6γ, 9.2γ, 10.0γ, 10.4γ, 11.1γ, and 12.2γ per 100 ml. of blood. Thus, the elevated SPI (above 7.0γ per 100 ml.) corroborated the impression of hyperthyroidism, and the response to treatment substantiated the diagnosis.

Problem Cases

Twenty-eight (30%) of the 90 patients presented problems of one sort or another. In eight instances it was not possible finally to conclude whether they were euthyroid or hyperthyroid. Two had SPI below 7.0γ, and six, above 7.0γ per 100 ml. In none of these were our observations sufficient to establish a final diagnosis (one patient died soon after admission; three were treated with propylthiouracil, and one was treated with strong iodine solution, U. S. P. [Lugol's solution], but no follow-up examinations were made, and three patients were discharged before we were able to complete our studies).

Thus, 20 of these 28 problem cases remained. It was possible to follow seven of these persons sufficiently so as to be able to conclude they were euthyroid. Three of these seven patients (SPI of 5.0γ, 6.0γ, and 6.2γ) had congestive heart failure associated with auricular fibrillation; initially it was difficult to be certain they were not thyrotoxic. However, all three responded promptly to therapy with digitalis and diuretics. Basal metabolic rates of +5% and —2% were subsequently obtained in two of the three, and there was nothing in their subsequent examinations to suggest hyperthyroidism. Two patients with SPI of 5.5γ and 4.9γ suffered from hypertension, and the possibility of hyperthyroidism was seriously entertained. In one the basal metabolic rate was +14% and the serum cholesterol was 225 mg. per 100 cc.; she was treated with from 450 to 600 mg. of propylthiouracil for two and one-half months without effecting a change in her clinical state in any respect; withdrawal of the drug also made no difference. The other patient had a serum cholesterol level of 257 mg. per 100 cc., and treatment with 450 mg. of propylthiouracil for three months was without benefit. The final two patients proved to be suffering from anxiety states. Their SPI levels were 5.5γ and 3.7γ per 100 ml. The former had a B. M. R. of +5%, a serum cholesterol level of 188 mg. per 100 cc., and slow resting pulse rates. There was nothing in their subsequent course which made us feel they were possibly thyrotoxic.

Finally, 13 of this "problem" group proved to be thyrotoxic; their SPI levels ranged from 7.1γ to 9.7γ per 100 ml. Twelve of these patients responded, unequivocally, to 300 to 600 mg. of propylthiouracil. One patient had a subtotal thyroidectomy. Detailed reviews of each of these cases does not seem necessary, because there was no question about the beneficial effects exerted by controlling the hyperthyroidism. In some the effects were surprisingly gratifying, especially in patients

who presented an indefinite clinical picture. One case may be cited as an example.

N. R., a 61-year-old man, suffered from troublesome paroxysmal auricular fibrillation; a very small firm adenomatous goiter was present, and clinically it was impossible to conclude whether or not he was euthyroid. His serum cholesterol level was 228 mg. per 100 cc., and a satisfactory basal metabolic rate could not be obtained. It was not possible to control the paroxysmal arrhythmia with either digitalis or quinidine. His SPI level was 7.8γ per 100 cc. After one month of treatment with 300 mg. of propylthiouracil per day, the cardiac symptoms disappeared, he gained some weight, and he felt generally well. He has remained asymptomatic for one year on no therapy other than the antithyroid drug.

Final Analysis of the Ninety Patients

A summary of the final diagnosis is outlined in the Table. It is seen that 65% of our cases proved to be euthyroid and 25%, hyperthyroid; no final conclusion could be reached in about 10% of the cases. These data represent the over-all picture of those hospitalized who had an adenomatous goiter. Since any patient who had an adenomatous goiter was included in the study, the data are not "loaded" in the direction of including mainly those who were thought to present a problem or who were thought to be hyperthyroid.

A more detailed summary of the data is presented in Figure 1. It is seen that the distribution of the SPI of those patients finally categorized as euthyroid is almost identical with our control, normal values. The mean value for the euthyroid patients with adenomatous goiters was 5.0γ per 100 ml.; the mean control value was 5.1γ per 100 ml. Further, it is of considerable significance that of the 23 patients finally categorized as hyperthyroid, 10 had SPI levels between 7.0γ and 8.0γ per 100 ml. Five had concentrations between 8.0γ and 9.0γ per 100 ml. Thus, more than one half had rather minimal elevations of SPI above normal (i. e., above 7.0γ per 100 ml.). In fact, only two patients had concentrations above 10.5γ per 100 ml. and the highest value was 12.2γ.

COMMENT

The difficulties in evaluation of the state of thyroid function in patients with adenomatous goiters has long been recognized. The ability of associated conditions such as heart disease to mask or overshadow the signs and symptoms of mild thyrotoxicosis, yet simultaneously be adversely affected by it, is well known. Of the 23 patients who were definitely proved to be hyperthyroid, in only 10 were the signs and symptoms of hyperthyroidism sufficiently definite to allow us to make an unequivocal diagnosis of hyperthyroidism prior to the administration of antithyroid drugs or prior to subtotal thyroidectomy.

It was our impression that in many of our thyrotoxic patients the hyperthyroidism had been present for a long time (in some, perhaps for years) without the patient being particularly aware of his difficulties. Why this should be so is not definitely known, although two possibilities seem likely. First, it may be

Summary of the Groups of Patients Which were Finally Categorized as Euthyroid or Hyperthyroid

Final Diagnosis	Original Category	Number of Cases	Per Cent of Total
Euthyroid	(1) Initially thought unequivocally euthyroid, and subsequent follow-up confirmed this impression	52	58
	(2) Those thought to present a problem in diagnosis; finally proved to be euthyroid	7	8
	Total euthyroid	59	65
Hyperthyroid	(1) Initially thought unequivocally hyperthyroid and subsequent follow-up confirmed this impression	10	11
	(2) Those thought to present a problem in diagnosis; finally proved to be hyperthyroid	13	14
	Total hyperthyroid	23	25
Unresolved cases	Total	8	9

that many of these patients become "acclimatized," at least to some extent and at least for a time, to their chronically altered state of metabolism. Subtle adaptions to a condition not completely out of control may occur. Second, one gains the impression that normal controlling mechanisms of thyroid function are still largely intact in these persons. The rapid and progressive disintegration of thyroid function observed in Graves' disease is not seen. The minimal elevations of the SPI values observed in our thyrotoxic patients supports this idea. Concentrations of SPI well above 12γ per 100 ml. are frequently seen in Graves' disease; not so, in the patient with the toxic adenomatous goiter. Further support for this idea is found in the report by Dobyns and Lennon,[3] who studied single and multiple thyroid adenomas by radioautographs. They concluded that

> adenomas which are functioning in excess of the remaining thyroid tissue may occur with or without an elevation in the basal metabolic rate [i.e., with or without clinical hyperthyroidism]. By their action they apparently suppress the function of the remaining thyroid tissue, depending on the magnitude of their contribution to the total biologic demand for thyroid hormone.

Thus, the toxic adenomatous goiter should represent "pure or primary" hyperthyroidism, and the situation should be entirely analogous to the results exhibited by the normal person given increasing amounts of exogenous thyroid hormone. Riggs and his associates[7] administered 3, 6, and 10 grains (180, 360, and 600 mg.) of dessicated thyroid to four euthyroid persons (Figure 2). There was a gradual increment in the SPI from normal levels so that at 6 grains per day the concentrations had risen just above normal; that is, between 7γ and 8γ per 100 ml. Even with 10 grains per day the maximal value was 13.1γ per 100 ml. The basal metabolic rate rose in a parallel fashion so that while on 6 grains per day the rates were approximately +5%, while the control values were approximately —15%. Physicians already recognize that fact that an accurate metabolic rate of +5 or +10% of normal may be highly significant and even indicative of hyperthyroidism in a person with suggestive signs of thyrotoxicosis. Similarly, we feel that an SPI above 7.0γ per 100 ml. should be regarded as an elevated value. Since small variations in SPI may normally occur from day to day (usually no more than 0.5γ), it is likely that even an SPI above 6.5γ should be regarded with some suspicion and the test repeated. Only 4.25% of our normal con-

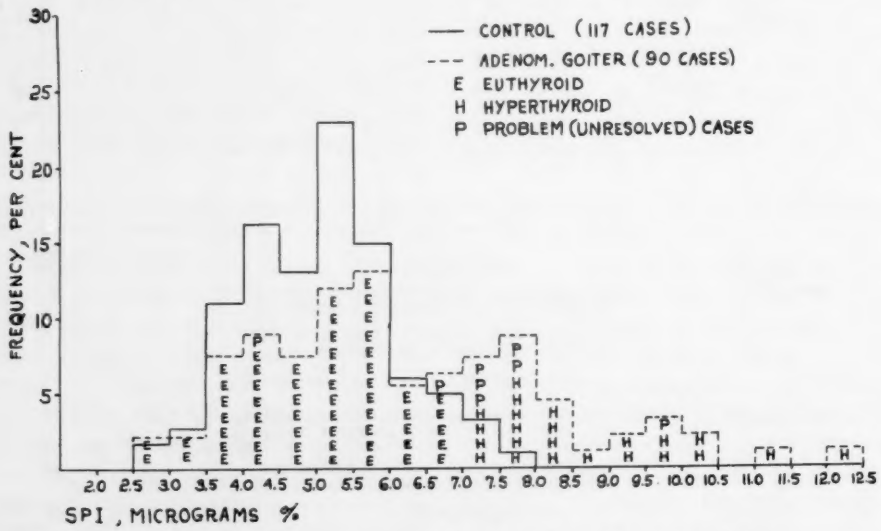

Fig. 1.—Frequency distribution of concentrations of SPI in 90 patients with adenomatous goiters and in 117 patients without thyroid disease.

trols had an SPI value between 7.0γ and 8.0γ per 100 ml. Therefore, to disregard an SPI above 7.0γ would do the patient an injustice.

Since the SPI is not influenced by as many extrathyroidal factors as is the basal metabolic rate and since it is difficult to obtain accurate values for metabolic rate the first time the test is performed in the elderly person, with or without complicating disease, it is our feeling that the SPI will prove to be of greater general value than the B. M. R. in appraisal of the total functional state of the adenomatous goiter. We are not in a position to evaluate radioiodine techniques in this problem. While we did our best to exclude the possibility, we did not encounter any definitely thyrotoxic patient who had an SPI below 6.9γ per 100 ml. However, final conclusions could not be reached in two patients with SPI levels of 4.4γ and 6.7γ. In any event, it appears that the occurrence of this phenomenon would be unusual. But, since we have already demonstrated [8] that the SPI is lowered in patients suffering from debilitating diseases, especially if associated with hypoalbuminemia, it would be possible that an occasional thyrotoxic patient might exhibit an SPI within the normal range.

SUMMARY

An effort was made to evaluate the status of thyroid function of 90 patients with adenomatous goiters. Many patients were old (mean age for the group was 64.1 years), and most were suffering from diseases other than thyroid disease. No patient with Grave's disease was included in this analysis. Sixty-five per cent (59 patients) were ultimately categorized as euthyroid; in these the serum precipitable iodine (SPI) varied from 2.5γ to 6.9γ per 100 ml. of blood (mean, 5.0γ). Ninety-one per cent of our patients without thyroid disease had a range of SPI from 3.5γ to 7.0γ (mean, 5.1γ).

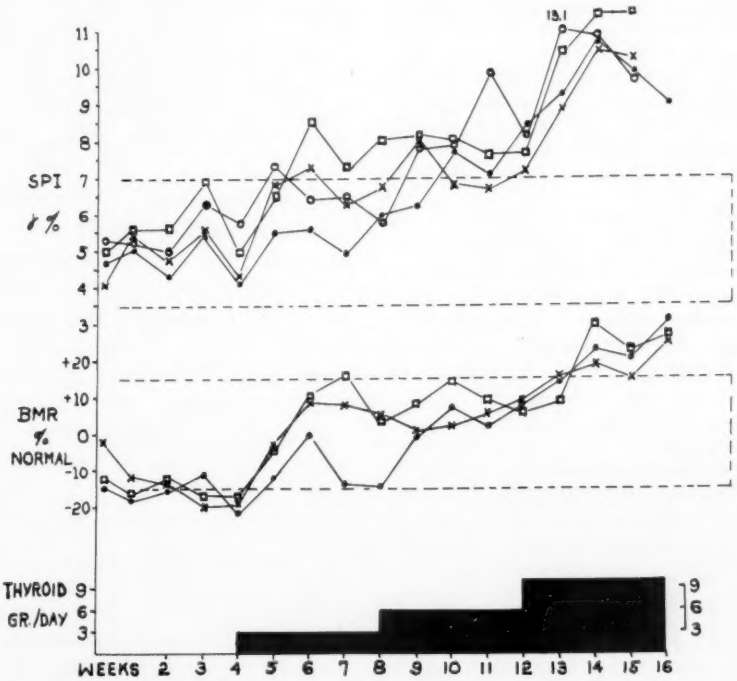

Fig. 2.—The effects of increasing doses of desiccated thyroid on the SPI and basal metabolic rate in four euthyroid patients. Each point represents a different determination. (Data redrawn and presented with permission from Riggs,[7] Journal of Clinical Investigation, Presbyterian Hospital, New York 32.)

Twenty-three patients definitely were proved to be hyperthyroid; more than half (15 patients) had only minimal elevations of SPI, i. e., values between 7.0γ and 9.0γ per 100 ml.

Our studies indicate that it would be a rare occurrence to find a hyperthyroid patient with an initial SPI below 7.0γ per 100 ml. and that it would be especially rare if below 6.5γ. Further, the finding of an SPI above 7.0γ usually indicates hyperthyroidism. Since most thyrotoxic patients with adenomatous goiters exhibit minimal elevations of SPI, it is incumbent upon the physician not to ignore even slightly elevated values. It is our impression that normal controlling mechanisms of thyroid function are largely intact in hyperthyroid patients with adenomatous goiters.

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Rheumatic Fever Activity Determination by Two Correlative Methods

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Two methods were employed in a study to ascertain whether the identification of a specific bacterial antigen or antibodies activated by it could be the means of determining rheumatic fever activity. The first method was by a hemolytic test with patient's serum as the antibody source and artificially sensitized sheep erythrocytes as the antigen. The second method was by an agglutination test using rabbit antiserum and patient's erythrocytes sensitized in vivo as the antigen. Clinical correlations were obtained with 78 rheumatic fever patients. There were 77 control cases. The methods proved practical in ascertaining rheumatic fever activity or quiescence and in distinguishing rheumatic fever from other disease processes.

The principle of a specific antigen-antibody reaction has been the basis of numerous tests to identify infectious diseases.* Erythrocytes that have been coated or sensitized by an antigen react with a specific antiserum prepared from that antigen to produce agglutination of the coated red cells.† When complement is added to this reaction, hemolysis occurs under certain conditions. Because the manifestations of rheumatic fever are associated with Group A beta-hemolytic Streptococcus, it was the purpose of this study to ascertain whether a means of identifying a specific bacterial antigen, or the antibodies elicited by it, could likewise determine rheumatic fever activity. It was postulated that the bacteria producing this tissue response possess a common antigen which is responsible for the manifestations of rheumatic fever.

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* References 1-10.

† References 3 and 11-20

METHODS OF STUDY

Two methods of determination were employed in this study. To demonstrate the presence of a specific antibody in the serum of rheumatic fever patients, sheep red cells were coated with heat-killed Group A beta-hemolytic streptococci, which had been isolated as the actual etiologic agents in active rheumatic fever patients. The coated red cells were then incubated with each patient's serum, and complement was added to produce hemolysis when the patient's serum contained the specific antibodies.

The second method employed Group A beta-hemolytic Streptococcus antiserum obtained by immunizing rabbits. The rheumatic fever patient's red cells were added to this antiserum to produce agglutination when the patient's cells were coated with the specific antigen.

Preparation of Antigen Media

Brain-heart infusion (Difco product), 37 gm., was dissolved in 1000 cc. of distilled water and sterilized in the autoclave at 15 lb. pressure (121 C) for 20 minutes. If the medium was not to be used the same day that it was sterilized, it was placed in flowing steam or boiling water for a few moments to drive off dissolved gases and cooled without agitation. Part of the brain-heart infusion was dispensed into small test tubes to which freshly washed sterile sheep cells were added so that each tube contained 10 cc. of a 0.5% cell suspension. The remaining brain-heart infusion was dispensed into larger test tubes to which sterile horse serum was added so that each tube contained 30 cc. of a 10% concentration of horse serum, or one part of horse serum to nine parts of brain-heart infusion. Regular blood agar plates were used to keep the stock cultures growing.

Preparation of Antigen for Injection

Cultures were transferred from the blood agar plates into tubes containing the brain-heart infusion

broth. Two loopfulls of bacteria from each plate were transferred to two tubes of brain-heart infusion broth with added horse serum. One tube of infusion broth containing sheep cells was inoculated in the same way. The sheep cells were to act as indicators to show when the new cultures contained enough active organisms to cause beginning hemolysis of the cells. At the time of hemolysis in the sheep cell system, the number of organisms present in the tubes of infusion broth with horse serum was considered to be adequate for preparation of the antigen.

The culture tubes were all incubated at 37 C. until hemolysis in the indicator system took place. This usually occurred in five hours. The bacteria that grew during this time were then washed three times with sterile buffered saline solution. The standard phosphate buffer was made up in sterile saline solution and Seitz-filtered. Final pH of the saline solution was 7.5.

Each tube of the broth containing the bacteria was centrifuged at 1500 rpm for 10 minutes, and the supernatant was removed under sterile conditions. Buffered saline solution, 10 cc., was added to each tube, and the tubes were again centrifuged. This procedure was repeated for each of the three washings.

The supernatant saline solution was discarded from the final washing, and the bacteria were pooled for use as an antigen. Several cultures were kept separate for a set of single antigens. These single antigens were also included in the pooled antigen.

The washed organisms were resuspended in sterile saline solution to make the concentration needed for injections.

Immunization Procedure

Adult male rabbits, weighing about 9 lb. each, were given eight injections as follows:

Pooled Organisms in Saline Solution, Cc.	
First injection	0.25
Second injection (4th day)	0.5
Third injection (8th day)	0.5
Fourth injection (11th day)	0.5
Fifth injection (16th day)	0.75
Sixth injection (19th day)	0.75
Seventh injection † (29th day)	0.5
Eighth injection (32nd day)	1

All animals received injections by the marginal ear vein.

† The seventh injection was decreased because there had been a lapse of 10 days since the previous injection.

Titration of Antibodies in Rabbit Sera Against Bacteria Antigens

Blood was drawn from rabbits by cardiac puncture, and the serum was separated from the clot by centrifugation. This serum was stored in sterile fire-sealed glass vials at 5 C. until it was used for testing. The serum was then inactivated at 56 C for half an hour. The agglutination tests were set up in 10 mm. by 75 mm. test tubes; 1 cc. serologic pipettes were used for measuring the serum, saline solution, and antigens. Serial twofold dilutions of each rabbit serum were made with sterile isotonic saline solution.

The antigens consisted of 17-hour cultures of the separate bacteria beta Streptococcus Group A, Type 5, Type 6, Type 12, and Type 19, grown in brain-heart infusion with added horse serum.

Each tube of the titration contained 0.5 cc. of rabbit serum which was diluted with saline solution, to which was added 0.5 cc. of a light suspension of bacteria in broth. The titrations were incubated at 37 C for two hours and were read for agglutination of bacteria. These readings were compared with a negative control tube containing the antigens in saline solution and broth. Normal rabbit sera were also used for titration as controls.

Agglutination Test: Rabbit Antiserum and Patient Cells

The rabbit antiserums had all the natural human red cell agglutinins adsorbed out by using packed washed human red cells of all blood types. One part packed cells was used to adsorb four parts rabbit serum for one or two hours at room temperature. This removed any agglutinins that might have been active against normal red cells at 37 C, room temperature, or 5 C.

The rabbit serums were then diluted with saline solution in serial twofold dilutions. The titrations were set up in 10 mm. by 75 mm. test tubes and separate 1 cc. serologic pipettes were used for the serum, cells, and saline solution. To each tube of the titration was added 0.1 cc. of the rabbit serum diluted with saline solution and 0.1 cc. of a 2% suspension of the patient's cells that had been treated with papain [21] or trypsin. The titration was incubated at 37 C. for half an hour and was read for agglutination of the red cells.

For screening purposes, tubes with undiluted rabbit serums in addition to patient's enzyme-treated cells were used. If these were positive, the titrations were done. Controls using normal rabbit sera were also employed.

Titers reported are all in terms of gross macroscopic agglutination, and the few end-points with microscopic-weak agglutination are reported in terms of the last tube showing macroscopic agglutination.

The cells of each patient were tested against a rabbit serum immunized with pooled antigen and one immunized against a single antigen. The titrations for both were done as described as well as with the modification of having washed cells as indicators rather than enzyme-treated cells.

Papain Procedure [21]

A stock solution of papain was made by suspending 1 gm. of papain in 100 ml. of 85% sodium chloride solution. This was kept in the refrigerator until the day it was used. Buffered saline solution was prepared by adding 1/15 M. Sorenson phosphate buffer, pH 7.3, to nine volumes of 0.85% sodium chloride solution. Nine volumes of buffered saline solution were added to one volume of stock papain to make the working papain solution. One milliliter of packed red cells, washed three times with saline solution, was added to 2 ml. of 0.1% buffered saline solution of papain. The cell suspension was incubated for 30 minutes in a water bath at 37 C, with frequent agitation. After centrifugation at moderate speed, the supernatant was removed. The papain-treated concentration of cells was washed three times with saline solution and then diluted to make a 2% suspension.

Hemolysin Titers Against Sensitized Sheep Cells

Titration.—Patient's serum was first adsorbed to remove all natural antisheep agglutinins. The serum was inactivated at 56 C for half an hour. Serial twofold dilutions were made with saline solution. To each tube of the titration were added 0.1 cc. dilution patient's serum with 0.1 cc. guinea pig complement diluted 1 : 10 and 0.1 cc. of a 0.5% suspension of sensitized sheep cells. Titrations were incubated at 37 C for two hours and were read for the presence of hemolysis.

Preparation of Sensitized Cells.—Seventeen-hour cultures of the antigens were grown in brain-heart infusion to which horse serum was added. These were centrifuged until the organisms were well packed at the bottom of the tube, and the supernatant was removed. The bacteria were washed three times with sterile saline solution. Organisms were killed by heating at 60 C for half an hour. The washed beta streptococci were then added to fresh sheep cells, one part bacteria to nine parts of sheep cells. These were incubated at 37 C for 30 minutes. The sensitized cells were then added to saline solution to make the 0.5% concentration used in the test.

Second Titration.—A second titration was set up in the same way, except that the sheep cells were treated with the enzyme papain before they were sensitized with beta Streptococcus antigens. Each titration had a negative control tube containing patient's serum and sheep cells which had not been sensitized. A second tube containing sensitized sheep cells and complement was used as a negative control.

Agglutination Titers Against Sensitized Sheep Cells

Patient's serum was inactivated at 56 C for half an hour after it had been adsorbed to remove all natural antisheep agglutinins. Serum was diluted with saline solution in serial twofold dilutions. To each tube of the titration was added 0.1 cc. diluted serum and 0.1 cc. of a 2% suspension of sensitized sheep cells. Titrations were incubated at 37 C for two hours and were read for agglutination. Control tubes were included containing patient's serum and normal sheep cells. Titrations were also incubated at room temperature for two hours.

Agglutinin and Hemolysin Titers of Sensitized Human Cells

The titrations were obtained as in the study of sensitized sheep cells, but here the indicator cells used were human red cells of different blood groups which had been sensitized by the same method as were the sheep cells. The negative control tube contained patient's serum and washed normal human cells.

LABORATORY RESULTS

The Group A beta-hemolytic streptococci used in preparing antisera in rabbits consisted of Types 5, 6, 12, and 19, each of which had been isolated from an active case of rheumatic fever. These four types were pooled as an antigen source; Types 5 and 12 were also used as single antigen sources. Antisera produced from both the single and pooled types were compared throughout the study, because of the theory that each of the types producing rheumatic fever also possesses a specific common antigen.

The rabbit Streptococcus antisera, both from the antigen of the pooled bacteria and from the single types, agglutinated the bacteria of each of the four types as well as the pooled suspension of all four types of bacteria. This occurred at a high titer (range, 1 : 640 to 1 : 2560), with slight variation among the separate types. All aggultination reactions continued to be demonstrable, although at a somewhat lower titer, after the sera were heat-inactivated and adsorbed with both human and sheep red cells. Normal rabbit sera as controls gave negative titers.

Sheep red cells were employed for the hemolysis determinations. An attempt was made to use human red cells for this reaction, and, although agglutination was constantly obtained, the addition of complement failed to produce hemolysis. Sheep red cells, on the other hand, elicited agglutination as well as hemolysis in high titers.

It was found that enzymatic (papain or trypsin) modification of the red cells in all methods enhanced the sensitivity of the reactions. Papain was the enzyme chosen for use in this study because of the ease and certainty in its employment.

EVALUATION OF REACTIONS

METHODS

I. Agglutination reaction: patient's red cells and beta-hemolytic Streptococcus rabbit antiserum
  A. Patient's cells washed with saline solution, plus
    1. Streptococcus antisera from pooled antigen source
    2. Streptococcus antisera from single antigen source
  B. Patient's cells washed with saline solution, then modified with papain, plus
  ‡ 1. Streptococcus antisera from pooled antigen source
    2. Streptococcus antisera from single antigen source

II. Agglutination reaction: patient's serum to which were added sheep cells sensitized with beta-hemolytic Streptococcus
  A. Patient's serum and sheep cells sensitized with the bacterial antigen and washed with saline solution
  B. Patient's serum and sheep cells modified with papin and sensitized with the bacterial antigen

III. Hemolysin reaction: patient's serum and sensitized sheep cells plus complement
  A. Patient's serum and sheep cells sensitized with the bacterial antigen and washed with saline solution; complement added
  ‡ B. Patient's serum and papain-modified sheep cells sensitized with bacterial antigen; complement added

‡ These methods were found to be most sensitive and consistent and are the ones reported in this study.

RESULTS

All the methods described were performed for each blood specimen. In general, it was found that those methods utilizing papain modification of the red cells were considerably more sensitive than those using washed cells; moreover, those methods employing rabbit Streptococcus antisera from a pooled antigen source were somewhat more sensitive than those employing antisera prepared from a single type bacterial source.

The data presented here concern only the two methods listed in the outline as I, B, 1 and III, B, since these were found to give the most sensitive and consistent results: The first of these methods employed an agglutination reaction using the patient's papain-treated red cells and a beta-hemolytic Streptococcus rabbit antiserum from a pooled antigen source. The second of the methods utilized a hemolytic reaction using the patient's serum and sheep cells modified by papain and further sensitized with specific bacterial antigen; complement was added to this system.

CLINICAL RESULTS AND DISCUSSION

The production of specific antisera for use in identifying disease etiology by tests employing hemagglutination and hemolysis has long been known. Recently it has been shown that enzymatic modification of red cells to which antigen is adsorbed will enhance the antigen-antibody response sensitivity of these coated cells.§ In the present study the enzyme papain was used and was found to enhance the sensitivity of both the agglutination and the hemolysin methods to such an extent that this method was chosen. Our methods therefore, differ fundamentally from that of Kirby,[24] who attempted to sensitize sheep cells with filtrates of Group A Streptococcus derived from a rheumatic fever patient, a crude extract containing group specific C, type specific M antigen, and streptolysin O substance. Kirby was unable to differentiate between acute rheumatic fever and acute Streptococcus infection. Our ag-

§ References 22 and 23.

glutination method utilized whole bacteria to sensitize sheep cells instead of extracts.

Seventy-eight hospitalized rheumatic fever patients at various stages of the disease process furnished 165 parallel determinations for both the hemolysin and the agglutination methods. Twenty-eight of these patients were tested initially within a period of six weeks after the onset of arthritic symptoms, and all were considered clinically to have active rheumatic fever at the time of testing. Eight were tested initially within the first week, three the second week, five the third week, two the fourth week, seven the fifth week, and three the sixth week. The results of the hemolysin studies showed that all 28 were positive in a titer of 1:4 or greater, and that 23, or 82%, had an initial titer of 1:8 or greater. The agglutination studies of this group showed that 25, or 90%, had an initial titer of 1:1 or above, and that 20, or 71%, had a titer of 1:2 or greater. One of the three negative specimens at the initial testing was obtained within the first week after the onset of arthritic symptoms and became positive in a titer of 1:16 during the second week after the onset of symptoms. The other two negative specimens at the initial testing were obtained at the third and fifth week, respectively, after the onset of arthritic symptoms.

The 165 determinations in the 78 rheumatic fever patients at various stages were correlated with the clinical status of the patient at the time of the test. The disease was classified clinically as active, stable, or inactive. The results obtained are recorded in Table 1.

The hemolysis method showed that 98% of those clinically considered active gave a positive reaction; of those clinically considered stable, 73% gave a positive reaction, and of those considered inactive 48% gave a positive reaction.

Results of the agglutination method revealed that 89% of those clinically considered active gave a positive reaction; 59% of those clinically considered stable gave a positive reaction, and of those considered inactive 30% gave a positive reaction.

The hemolysis method gave higher titers in general (Table 1), as well as a somewhat greater degree of correlation in the clinically active and stable phases of the disease process.

Eight of the 165 agglutination determinations and three of the 165 hemolysis determinations were negative at a time when the rheumatic fever was clinically considered to be active (Table 2). These results were obtained in 10 blood specimens from nine different patients. Further investigation of these patients showed that one patient was tested within the first week of the disease process and became highly positive by the second week; the disease in seven, although considered still to be active, was in the process of subsiding, as evidenced by subsequent clinical studies. One patient had a negative reaction by both methods at the time he was first seen, in the 10th week after the onset of symptoms, but at the next testing, one week later, gave positive results by both methods. His tests then became negative again as the disease process became clinically stable.

TABLE 1.—*Classification of Seventy-Eight Patients and Titers in 165 Determinations*

Clinical Status	Titers							Total Determinations
	Negative	1:1	1:2	1:4	1:8	1:16	1:32	
Hemolysis								
Active	3	.....	3	15	23	26	5	75
	4.0%	.....	4.0%	20.0%	30.6%	34.7%	6.7%	
Stable	12	.....	9	6	7	9	1	44
	27.2%	.....	20.5%	13.6%	16.0%	20.5%	2.2%	
Inactive	24	.....	7	9	3	3	.....	46
	52.2%	.....	15.2%	19.7%	6.5%	6.5%	.....	
Agglutination								
Active	8	8	21	27	8	2	1	75
	10.7%	10.7%	28.0%	36.0%	10.7%	2.6%	1.3%	
Stable	18	.....	18	8	.....	.....	.....	44
	41.0%	.....	41.0%	18.0%	.....	.....	.....	
Inactive	32	2	8	3	1	.....	.....	46
	69.6%	4.3%	17.4%	6.5%	2.2%	.....	.....	

All but two of those patients classified as having clinically active rheumatic fever and a negative reaction by either or both methods were observed to be in a subsiding phase. This may indicate that in some patients the titers become negative a short time prior to the complete disappearance of the clinical manifestations.

Twenty-five of the 78 patients were followed with serial parallel determinations of both the hemolysin and the agglutination methods from a time when one or both methods were positive until one or both methods became negative. As is evident from Table 3, the hemolysin titers generally tended to be somewhat higher than the agglutination titers. There was seen to be an excellent correlation between the clinical status of the disease process and the test results, as the disease gradually became inactive.

In the group of patients tested initially within the first six weeks of the disease, all had a positive reaction by the hemolysin method, and all but two, by the agglutination method. As the disease process became inactive, the titers of both test methods became lower and gradually became negative at approximately the same time as the disease became clinically inactive.

Although excellent correlation was observed between the clinical status of the disease and the titers obtained by both methods, the heights of the titers were not indicative of the extent of pathologic involvement or of the prognosis. It is evident that the classification of patients by clinical criteria is subject to individual variation.

Of particular interest and worthy of emphasis is the absence of correlation between the titers of either method and the sedimentation rate.

Therapy with antibiotics, steroids, or salicylates evidently did not interfere with determinations in any way, although it is of interest that sodium salicylate and other related compounds, as well as cortisone, have been reported to inhibit certain antigen-antibody reactions. This mechanism is believed due to an increased solubility of the antigen-antibody complex, with both the anti-protein and antipolysaccharide systems being affected.[25] This may also serve as a partial explanation for the efficacy of such therapy in rheumatic fever.

It is noteworthy that certain plasma fractions, including those of human sera under certain conditions [20] are thought to be capable of inhibiting modification of red cells by bacteria.

TABLE 2.—*Negative Titers Prior to Complete Disappearance of Symptoms* *

Patient	Week After Onset of Symptoms; Negative Hemolysis Test Obtained	Week After Onset of Symptoms; Negative Agglutination Test Obtained	Previous or Subsequent Parallel Hemolysis Determinations Show Titers	Previous or Subsequent Parallel Agglutination Determinations Show Titers	Number of Weeks After Negative Test Until Disease Clinically Stable	Clinical Evaluation of Patient Prior to and Subsequent to Negative Determination Indicates Disease Process
P. R.	12th	...	.....	Subsiding	2	Subsiding
T. W.	....	5th	Subsiding	Previously positive	1	Subsiding
P. S.	....	6th	Subsiding	Previously positive	..	Subsiding
J. J.	....	1st	Positive	Subsequently positive	..	Acute
J. K.	....	5th	Subsiding	.....	4	Subsiding
P. R.	....	8th	Subsiding	Previously positive	..	Subsiding
P. C.	10th	...	Previously positive	Subsiding	2	Subsiding
M. C.	....	3d 6th	Subsiding Subsiding	....	4 2	Subsiding Subsiding
M. M.	10th	10th	Subsequently positive	Subsequently positive	3	Subsiding

* Subsequent findings in eight patients with negative agglutinations and three patients with negative hemolysin reactions whose disease was considered active at the time determinations were performed.

TABLE 3.—*Agglutination and Hemolysis Methods in Twenty-Five Patients Followed from the Acute Phase to Convalescence*

Patient	Weeks After Onset of Symptoms	Agglutination Titer	Hemolysin Titer	Sedimentation Rate	Antistreptolysin O, Units	Presence of β-Hemolytic Streptococcus in Throat Culture	Therapy Other Than Antibiotics	Presence of First Degree Heart Block	Rheumatic Involvement	Clinical Status
J. J.	1	Negative	1:16	46	....	+	None	..	Cardiac and joint	Active
	2	1:16	1:16	46	....	..	ASA*	..	Cardiac and joint	Active
	3	1:8	1:8	47	2500	..	ASA	..	Cardiac and joint	Active
	4	1:4	1:8	..	....	..	.....	..	Cardiac and joint	Active
	5	1:4	1:2	40	1250	..	.....	..	Cardiac and joint	Stable
	6	Negative	Negative	..	....	..	.....	..	Cardiac and joint	Inactive
T. W.	1	1:1	1:16	49	2000	..	ASA	..	Cardiac and joint	Active
	2	1:32	1:16	31	....	+	ASA	..	Cardiac and joint	Active
	3	1:16	1:16	..	1250	..	ASA	..	Cardiac and joint	Active
	4	1:2	1:4	45	....	..	ASA	..	Cardiac and joint	Active
	5	Negative	1:2	..	1250	..	Cortisone ASA	..	Cardiac and joint	Active
	6	Negative	Negative	..	....	..	Cortisone ASA	..	.....	Stable
M. B.	5	1:8	1:8	39	....	..	.....	..	Cardiac	Active
	6	1:4	1:8	..	....	..	.....	..	Cardiac	Active
	7	1:4	1:4	24	....	..	.....	..	Cardiac	Active
	8	Negative	1:2	21	....	..	.....	..	Cardiac	Stable
	9	Negative	Negative	19	....	..	.....	..	Cardiac	Inactive
P. C.	12	1:4	1:8	12	....	..	Compound F†	..	Cardiac and joint	Active
	13	1:2	Negative	2	....	..	Compound F	..	Cardiac and joint	Active
	15	1:2	Negative	2	....	..	Compound F	..	Cardiac and joint	Stable
	18	Negative	Negative	..	....	..	.....	..	Cardiac and joint	Inactive
	20	Negative	Negative	..	....	..	.....	..	.....	Inactive
D. B.	12	1:4	1:32	40	....	..	Cortisone	..	Cardiac and joint	Active
	13	1:4	1:8	..	....	..	Cortisone	..	Cardiac and joint	Active
	18	Negative	1:4	..	....	..	.....	..	.....	Stable
	21	Negative	Negative	..	....	..	.....	..	.....	Stable
	22	Negative	Negative	..	....	..	.....	..	.....	Inactive
L. V.	3	1:4	1:16	..	....	..	ASA	..	Cardiac and arthritis	Active
	4	1:4	1:8	..	....	..	.....	..	Cardiac and arthritis	Active
	5	1:2	1:1	..	....	..	.....	..	Cardiac and arthritis	Stable
	6	Negative	Negative	26	....	..	.....	..	Cardiac and arthritis	Inactive
L. T.	12	1:2	1:2	4	....	..	.....	..	Arthritis	Stable
	13	1:4	1:16	..	....	..	.....	..	.....	Stable
	14	1:2	1:8	4	....	..	.....	..	.....	Inactive
	17	Negative	1:4	..	....	..	.....	..	.....	Inactive
M. C.	3	Negative	1:4	47	....	..	.....	+	Cardiac and arthritis	Active
	6	Negative	1:2	31	....	..	.....	+	.....	Active
	8	Negative	Negative	26	....	..	.....	..	.....	Stable
	10	Negative	Negative	20	....	..	.....	..	.....	Inactive
J. S.	14	1:4	1:8	15	....	..	.....	..	Cardiac	Active
	15	1:8	1:4	15	....	..	.....	..	.....	Active
	16	1:4	1:16	20	....	..	.....	..	.....	Active
	17	1:1	Negative	17	....	..	.....	..	.....	Inactive

TABLE 3.—*Agglutination and Hemolysis Methods in Twenty-Five Patients Followed from the Acute Phase to Convalescence—Continued*

Patient	Weeks After Onset of Symptoms	Agglutination Titer	Hemolysin Titer	Sedimentation Rate	Antistreptolysin O, Units	Presence of β-Hemolytic Streptococcus in Throat Culture	Therapy Other Than Antibiotics	Presence of First Degree Heart Block	Rheumatic Involvement	Clinical Status
M. M.	10	Negative	Negative	..	....	..	Cortisone	..	Cardiac and arthritis	Active
	11	1:8	1:8	..	....	..	Cortisone	..	.....	Active
	12	Negative	Negative	25	....	..	Cortisone	..	.....	Stable
	17	Negative	Negative	..	....	..	.....	..	.....	Stable
G. F.	13	1:1	1:2	..	....	..	ASA	..	Cardiac and arthritis	Active
	16	Negative	Negative	..	....	..	ASA	..	.....	Stable
	29	Negative	Negative	..	....	..	.....	..	.....	Inactive
	23	Negative	Negative	..	....	..	.....	..	.....	Inactive
K. B.	3	1:4	1:16	23	....	..	.....	..	Cardiac and arthritis	Active
	8	Negative	1:4	16	....	..	Cortisone	..	.....	Stable
	9	Negative	Negative	12	....	..	.....	..	.....	Inactive
M 3027	15	1:4	1:6	..	....	..	.....	..	Cardiac and chorea	Stable
	17	1:2	1:8	..	....	..	.....	..	.....	Inactive
	18	Negative	1:4	9	....	..	.....	..	.....	Inactive
R. K.	6	1:4	1:4	9	....	..	Cortisone	..	Cardiac	Active
	10	1:2	1:4	..	....	..	.....	..	.....	Stable
	11	Negative	1:2	11	....	..	.....	..	.....	Inactive
A. S.	1	1:2	1:4	46	....	..	ASA	.	Cardiac and arthritis	Active
	3	1:2	1:8	42	1250, 2 wk.	..	.....	..	Cardiac and arthritis	Stable
	4	Negative	Negative	..	....	..	.....	..	.....	Inactive
D. R.	2	1:2	1:8	26	....	..	ASA	..	Cardiac and arthritis	Active
	3	1:2	1:4	..	....	..	.....	..	.....	Stable
	4	Negative	Negative	..	....	..	.....	.	.....	Inactive
D. J.	1	1:2	1:8	..	....	..	.....	..	Subcutaneous nodes, cardiac, and arthritis	Active
	5	1:2	1:4	..	....	..	.....	..	.....	Inactive
	6	Negative	Negative	..	....	..	.....	..	.....	Inactive
A. Z.	31	1:2	1:4	..	....	..	ASA	..	Erythema multiforme (marginatum) and cardiac	Active
	37	Negative	1:2	..	....	..	ASA	..	.....	Stable
	39	Negative	Negative	16	....	..	.....	..	.....	Inactive
C. M.	15	1:4	1:16	..	....	+	Cortisone	.	Cardiac and arthritis	Active
	17	1:2	1:2	35	....	+	.....	..	.....	Stable
	21	Negative	Negative	..	....	..	.....	..	.....	Inactive
P. R.	12	1:8	Negative	41	....	..	.....	..	Cardiac and arthritis	Active
	17	1:4	Negative	38	....	..	.....	..	.....	Stable
	18	Negative	Negative	35	....	..	.....	..	.....	Inactive
T. S.	5	1:4	1:16	12	....	+	ASA	..	Cardiac	Active
	13	Negative	1:2	8	....	..	.....	..	.....	Inactive
F. C.	3	1:4	1:16	..	....	..	ASA	..	Cardiac and arthritis	Active
	4	Negative	1:4	43	....	..	.....	..	.....	Inactive
R. K.	7	1:4	1:16	28	....	..	.....	..	Cardiac and arthritis	Active
	8	Negative	1:4	31	....	..	.....	..	.....	Stable
G. T.	6	Negative	1:16	16	....	..	ASA	..	Cardiac and arthritis	Active
	7	Negative	1:2	12	....	..	ASA	..	.....	Stable
W. G.	5	1:4	1:8	22	....	..	ASA	..	Cardiac and arthritis	Active
	12	Negative	Negative	42	....	..	ASA	..	.....	Stable

* Acetylsalicylic acid.
† 17-hydroxycorticosterone.

CONTROLS

A total of 77 control cases was studied by both the hemolysin and the agglutination methods. As is evident in Table 4, beta Streptococcus was obtained in culture in 13 of these cases, and alpha Streptococcus, in 20. All patients in the control group gave a negative reaction to both methods of determination.

SUMMARY AND CONCLUSIONS

The principle of the antigen-antibody reaction has been the basis for numerous tests to identify infectious diseases. It has also been shown that erythrocytes which have been coated with an antigen are agglutinated when antiserum prepared from this coating antigen is added. When complement is added to this system, under certain conditions, hemolysis occurs. Because rheumatic fever is associated with tissue reaction to Group A beta-hemolytic Streptococcus, it was the purpose of this study to determine whether a means of identifying a specific bacterial antigen, or antibodies elicited by it, could be the means of ascertaining rheumatic fever activity.

Two methods of determination were employed: In one method serum of rheumatic fever patients was used as the antibody source; as the antigen source, sheep red cells, coated with heat-killed Group A beta-hemolytic streptococci, which had been isolated from active rheumatic fever patients, were used; complement was added to produce hemolysis. The other method utilized, as the antibody source, Group A beta-hemolytic Streptococcus antiserum obtained from rabbits; for the antigen source erythrocytes of rheumatic fever patients, exposed to the antigen for coating in vivo, were used in an agglutination test.

In most instances the hemolysis method, using patients' serum as the antigen source, was found to be somewhat more sensitive; in both methods, treating erythrocytes with papain was found to enhance the reaction.

Control studies of 77 varied patients including those from which alpha- and beta-hemolytic streptococci were isolated, showed no instances in which other disease processes interfered with either test method. This would indicate an excellent specificity of these tests in active rheumatic fever.

Clinical correlations were obtained for 78 rheumatic fever patients, most of whom were tested at intervals of the disease process. The titers in both test methods were elevated within the first few days of the active process in most cases, and they then gradually sub-

TABLE 4.—*Negative Controls*

	Positive Cultures, No.		Cases Studied, No.	Agglutination Test	Hemolysis Test
	Alpha Streptococcus	Beta Streptococcus			
Pneumonia	2	1	14	Negative	Negative
Rheumatoid arthritis	..	..	12	Negative	Negative
S. B. E.*	9	1	10	Negative	Negative
Throat infections	2	9	9	Negative	Negative
Other Streptococcus infections	5	..	5	Negative	Negative
Nephritis	..	..	5	Negative	Negative
Lupus erythematosus	..	..	4	Negative	Negative
Measles	1	..	3	Negative	Negative
Chicken pox	1	..	3	Negative	Negative
Scarlet fever	..	2	4	Negative	Negative
Mumps	..	..	1	Negative	Negative
Hyperthyroidism and measles	..	..	1	Negative	Negative
Diarrhea due to Shigella Flexner	..	..	1	Negative	Negative
Amebiasis	..	..	1	Negative	Negative
Cellulitis (postauricullar)	..	..	1	Negative	Negative
Tuberculous epididymitis	..	..	1	Negative	Negative
Dermatitis venenata (mercurial sensitivity)	..	..	1	Negative	Negative
Mercury ingestion	..	..	1	Negative	Negative

* S. B. E., subacute bacterial endocarditis.

sided and disappeared as the process became inactive. The results also indicated an excellent correlation between the test results and the clinical status of the disease, although the height of the titer was not indicative of the severity of the process.

It is concluded that these methods are of practical value in ascertaining activity or quiescence of a rheumatic fever process, as well in distinguishing rheumatic fever from other disease processes with similar clinical manifestations.

Dr. Hugh McCulloch, Medical Director, La Rabida Sanitorium, Chicago, and the Staff of the Childrens' Division of the Cook County Hospital cooperated in this study.

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Clinical Evaluation of Puromycin in Human Neoplastic Disease

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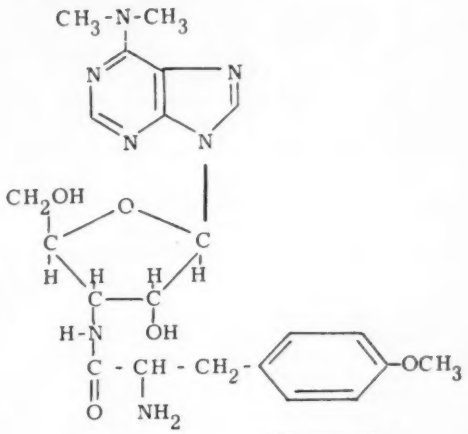
Puromycin (Stylomycin) * is an antibiotic obtained from a species of actinomycete, Streptomyces albo-niger.† In addition to its inhibitory action on some Gram-positive and Gram-negative bacteria and on Trypanosoma equiperdum, Trypanosoma cruzi, and Trypanosoma gambiense,‡ it was found to have inhibitory activity against certain tumors.§ Puromycin shows appreciable inhibition against the mammary adenocarcinoma of the C3H mouse, the mammary adenocarcinoma 755 of the C57BL mouse, and a glioblastoma cultivated in the chick embryo.

The structure, chemical properties, and synthetic studies of puromycin have been reported by Waller and co-workers [8] and Baker and his co-workers.[9] Puromycin is



Puromycin.

Figure 1.

6-dimethylamino-9-(3′-*p*-methoxy-L-phenylalanylamino-3′-deoxy-D-ribosyl)-purine (Fig. 1).

Toxicity studies in mice indicate the LD_{50} values of puromycin to be 360 mg/kg. intravenously, 520 mg/kg. intraperitoneally, and 678 mg/kg. orally. Loss of weight was produced by the antibiotic in the mouse. In rats receiving repeated dosages of 25 to 100 mg/kg. parenterally from one to four weeks, evidence of kidney damage was observed. Toxicity manifestations in rats receiving high dosages of puromycin for five to six weeks were marked edema of the soft tissues, ascites, thick cloudy sticky urine, pale mottled enlarged kidneys, and small white spleen.

As puromycin produced an inhibitory action on certain animal tumors, it was used in this study to determine its effects on human tumors.

Puromycin was administered to 51 patients with incurable neoplastic diseases. The types of cases included in this study are indicated in Table 1.

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† References 1 and 2.

‡ References 1 and 3-5.

§ References 6 and 7.

The patients included in this study were beyond the hope of cure with surgery and radiation therapy. In all cases, the diagnoses were established by histological examination prior to treatment. Pretreatment and follow-up examinations consisted of frequent observations of the patient for subjective and objective changes, with particular emphasis upon any change in the size, visible or palpable, of tumor masses. All nonbedridden patients were weighed at weekly intervals. Repeat biopsies, bone marrow studies, complete blood studies, urinalyses, x-rays, photographs, and other necessary procedures were performed as often as possible and as frequently as deemed necessary in the particular case. The following blood chemistry studies were repeated at monthly intervals, more often when indicated: determinations of sugar, urea nitrogen, icteric index, bilirubin, thymol turbidity, total protein, albumin, phosphorus, alkaline phosphatase, acid phosphatase, and calcium. Palliative surgery was performed when indicated. Antibiotics, transfusions, infusions, narcotics, and vitamins were given as part of the total care of the patients. Every effort was made to maintain the nutritional status, comfort, and feeling of well-being of each patient.

TABLE 1.—*Cases of Incurable Neoplastic Diseases Treated with Puromycin*

Diagnosis	Cases, No.
Carcinoma of mouth	2
Carcinoma of esophagus	2
Carcinoma of stomach	2
Carcinoma of cecum	2
Carcinoma of sigmoid	3
Carcinoma of rectum	4
Carcinoma of anus	1
Carcinoma of gall bladder	1
Carcinoma of lung	3
Carcinoma of bladder	1
Carcinoma of prostate	6
Carcinoma of penis	1
Carcinoma of breast	11
Carcinoma of cervix	5
Carcinoma of skin	2
Metastatic carcinoma, primary site undetermined	3
Hodgkin's disease	2
Total	51

Three of the patients (Cases 30, 36, and 41) included in this series had previous radiation therapy given 8 months, 4 years, and 13 months, respectively, prior to therapy with puromycin. One patient (Case 50) received radium 15½ months prior to puromycin therapy.

Nineteen of the 51 patients included in this series had major surgery for the removal of their primary tumor prior to the institution of chemotherapy with puromycin. Seven patients (Cases 1, 11, 26, 29, 34, 36, and 39) who had radical mastectomies for carcinoma of the breast subsequently returned to the hospital with metastases. At this time puromycin therapy was started. The puromycin was instituted in these patients five months to four years, nine months following their operations. Six patients (Cases 4, 7, 19, 24, 27, and 28) had resections of the colon or rectum for neoplastic tumors of these regions 66 days to 1 year, 9 months prior to puromycin therapy. Three patients (Cases 14, 43, and 44) had prostatectomies and orchiectomies for carcinoma of the prostate 1 year, 109 days to 7 years, 5 months prior to therapy with puromycin. Two patients (Cases 3 and 31) with carcinoma of the prostate had orchiectomies performed 4 years and 5 years, 11 months prior to puromycin therapy. In one patient (Case 37) a radical excision for epidermoid carcinoma of the skin over the sacral area was performed 11½ months prior to drug therapy. Except for two patients who underwent exploratory laparotomies and one who had a gastrostomy, the other 32 cases in the series had only biopsies of their tumors and no major surgery.

Hormone therapy or chemotherapy had been given to nine patients included in this study prior to therapy with puromycin. The beneficial effect, if any, from hormone or chemotherapy had apparently ceased in this group of patients prior to institution of puromycin treatment. The patient with carcinoma of the penis (Case 10) received corticotropin for 77 days prior to chemotherapy. The patient with carcinoma of the mouth (Case 40) received Wright-West dog duodenal extract (WWDD) for two months prior to puromycin therapy. Two patients with carcinoma of the prostate (Cases 31 and 44) received estrogen therapy for a period of 5 weeks and 3 months, respectively, terminating 5 years, 10 months and 13 months prior to puromycin therapy. Testosterone was administered to one patient (Case 36) with carcinoma of the breast for four months prior to chemotherapy. Another patient with carcinoma of the breast was treated with 4-amino-N^{10}-pteroyl glutamic acid (amethopterin) for five months prior to therapy with puromycin. Amethopterin was administered to one patient with carcinoma of the bladder (Case 45) for six months prior to puromycin. Two patients with Hodgkin's disease (Cases 42 and 47) were treated with triethylene phosphoramide for a period of seven months prior to puromycin therapy in one case and for five months, ending two months prior to puromycin therapy, in the second case. Case 47 also received cortisone for two weeks prior to and during puromycin therapy.

Of the 51 patients treated with puromycin in this series, 45 have died, 4 were lost to study, and 2 are living and still under study. The age of patients treated with puromycin ranged from 25 years to 88 years. Twenty-seven were women, and 24 were men.

TABLE 2.—*Summary of Clinical Results with Puromycin*

Case No. C. R. No.	Age and Sex	Diagnosis	Prior Therapy, Surgery, Radiation, Etc.	Puromycin: Daily Oral Dose, Mg.	Puromycin: Total Dose, Mg.	Puromycin: Total Duration of Therapy	Condition at Onset of Therapy	Clinical Response
1 223	47 F	Carcinoma of breast with metastasis (duct-cell)	Biopsy of breast, then radical mastectomy 4½ mo. prior to therapy	5-1,000	29,930	64 days	Subcut. nodules over left anterior chest; ulceration of skin at site of old operative scar; old left radical mastectomy; bone metastasis; node in left axilla; general condition fair	While under therapy, the skin metastases increased in size and number; bone pain occurred and increased; bone metastases increased in size and number; after 64 days of therapy patient developed white frost on face, became disoriented, drug stopped; 4 days later patient became comatose and died, 68 days after onset of therapy
2 287	80 F	Carcinoma of cecum (adenocarcinoma)	Exploratory laparotomy and partial resection left lobe of liver 16 days before drug therapy	250-750	10,500	Over a period of 20 days, received drug 18 days	Fair; right lower quadrant mass size of tennis ball; abdominal pain	After patient had taken drug 8 days, she started vomiting frequently; when drug discontinued, vomiting stopped the following day; when drug resumed, vomiting resumed; patient was changed to another form of chemotherapy; no change in size of mass in right lower quadrant or general condition under therapy; died 135 days after onset of therapy
3 237	63 M	Carcinoma of prostate	Orchidectomy 1947, 4 yr. prior to drug therapy	250-1,000	53,250	Over a period of 125 days, received drug 111 days	Poor; bone metastasis; general pain, especially back and legs; swelling of right leg; large inguinal nodes; fibrotic infiltration of lungs and large right hilar mass	General condition remained poor throughout treatment and patient went gradually downhill and died 142 days after onset; decrease in size of right hilar mass 2 mo. after therapy; bone sclerosis on repeated x-rays unchanged during therapy; temporary increase then decrease in alkaline phosphatase; temporary increase then decrease in acid phosphatase
4 325	35 F	Carcinoma of anus (epidermoid)	Abdominal perineal resection 66 days prior to drug therapy	250	14,250	57 days	Poor; palpable and visible fungating masses left lower quadrant; fecal fistula; ulcer on buttocks; partial obstruction	During 1st mo. of therapy palpable and visible tumor masses in left lower quadrant became smaller; during the 3d wk. of therapy the 2 fungating masses which were visible sloughed away in the center and coalesed; during the 6th wk. mass in left lower quadrant became larger; patient became drowsy and died 58 days after therapy was begun
5 293	66 F	Carcinoma of rectum (adenocarcinoma)	Liver biopsy 23 days prior to therapy	250	11,250	45 days	Poor; large liver; fluid in right chest; peripheral edema	Patient went slowly and progressively downhill; died 45 days after onset of therapy
6 280	66 M	Carcinoma of esophagus	Biopsy of esophagus lesion, gastrostomy 46 and 16 days prior to chemotherapy	750	12,000	16 days	Poor; gastrostomy	Went downhill and died 16 days after onset of therapy
7 240	55 F	Carcinoma of sigmoid	Resection of sigmoid tumor 7 mo. prior to therapy	1,000	15,000	15 days over 21-day period	Rectal mass; large liver, mass in left lower quadrant; infiltration right lower lobe; general condition poor	Condition unchanged during therapy with puromycin; owing to daily vomiting, drug was stopped and patient was changed to another form of therapy; died 103 days after therapy was begun
8 326	59 F	Carcinoma of breast	None	500	3,000	6 days	General condition very poor; consolidation in left lung; large ulcerated tumor in right breast; swelling of right arm; enlarged axillary nodes; shortness of breath	Condition unchanged in breast lesion or nodes; patient went downhill and died 7 days after therapy started
9 307	49 M	Carcinoma of gall bladder (papillary cystadenocarcinoma)	Biopsy of cervical node 12 days prior to therapy; liver biopsy	500	2,000	4 days	Jaundice; large irregular liver; pulmonary infiltration; general condition poor	No change in condition; died suddenly 5 days after therapy was started

TABLE 2.—*Summary of Clinical Results with Puromycin*—Continued

Case No. C. R. No.	Age and Sex	Diagnosis	Prior Therapy, Surgery, Radiation, Etc.	Puromycin: Daily Oral Dose, Mg.	Puromycin: Total Dose, Mg.	Puromycin: Total Duration of Therapy	Condition at Onset of Therapy	Clinical Response
10 281	77 M	Carcinoma of penis (epidermoid)	Corticotropin for 77 days prior to puromycin	750	31,500	42 days	Poor; associated hemiplegia, hypertension, arteriosclerosis, and urethral stricture	17 days after onset of therapy definite decrease in penile lesion observed; lesion continued to decrease in size progressively until 5 days before death, when lesion increased slightly in size; patient went into uremia and died 45 days after onset of therapy
11 310	47 F	Carcinoma of breast	Right radical mastectomy 1 yr. prior to therapy; hysterectomy 11 yr. prior to therapy	500	2,000	4 days	Very poor; pleural effusion; large liver; breast mass; large nodes	No change; patient in very poor condition; went downhill and died 5 days after onset of therapy
12 254	69 M	Carcinoma of stomach (adenocarcinoma)	Biopsy of cervical node 6 days before therapy	750	27,400	42 days over period of 50 days	Stricture of urethra; hypertension; left supraclavicular nodes enlarged; large liver	Patient developed urinary obstruction, then intestinal obstruction and died 51 days after therapy; supraclavicular node remained same size under therapy
13 243	46 M	Carcinoma of lung	Biopsy of lesion in bronchus; biopsy of cervical node; biopsy of esophagus lesion	1,000	6,000	6 days	Very poor; pulmonary infiltration; esophageal lesion; large inguinal nodes	General condition poor; patient went downhill and died 17 days after therapy was begun
14 277	56 M	Carcinoma of prostate	Prostatectomy and orchidectomy 1949; corticotropin for 69 days prior to puromycin	750	21,000	28 days	Poor; bone metastasis; pulmonary fibrosis; small inguinal nodes	Patient went progressively downhill and died 29 days after therapy was begun
15 285	44 M	Carcinoma of esophagus	Smear from esophagus lesion; cervical node biopsy	750	2,250	3 days	Very poor; mass in chest and deformity of lower third esophagus	Patient went downhill and died 4 days after therapy was begun
16 320	45 F	Carcinoma of cervix (epidermoid)	Biopsy of cervix 9 mo. prior to therapy	250	6,500	26 days	Frozen pelvis; suprapubic mass; general condition poor; in uremia	Patient's frozen pelvis and suprapubic mass unchanged; general condition poor at onset of therapy; in uremia; 22 days after onset of therapy, frost noticed on face; drug stopped and patient died 29 days after onset of therapy
17 244	46 M	Carcinoma of lung (adenocarcinoma)	Biopsy subcut nodule 3 days prior to therapy	750-1,000	28,750	34 days	Fair; pulmonary lesion, right upper lobe; subcut. metastasis; cervical nodes	After 1 wk. of therapy, questionable slight decrease in size of subcutaneous metastasis; after 2 wk. still some questionable decrease in size of subcutaneous metastasis, but increased pain in left hip occurred; after 3 wk. increase in size of cervical and chest masses occurred; drug increased to 1 gm. daily; patient started vomiting and having diarrhea; this stopped 1 day after drug was stopped; no change in tumor masses on 1 gm. daily; during puromycin therapy patient noted that little swellings on knuckles and on 2d interphalangeal joints of fingers disappeared, and that he was able to close hands completely; the swellings had been present 8-9 mo.; owing to gastrointestinal disturbances, patient changed to another form of therapy; died 120 days after therapy was begun

18 284	46 M	Carcinoma of prostate	Transurethral biopsy	750	16,500	22 days	Poor; abdominal and back pain; associated prostate abscess; hematuria	No essential change; patient died 23 days after onset of therapy; no change in x-rays of bone metastasis under therapy
19 249	60 F	Carcinoma of sigmoid (adeno-carcinoma)	Laparotomy and anterior resection	750	28,500	38 days over 60 days	Poor; ascites; masses in right upper quadrant and lower left quadrant; uremia; pulmonary infiltration	During first 5 wk. of therapy patient appeared and felt generally better, a definite decrease in ascites, softening of abdomen, and softening of palpable abdominal masses was observed; no change in size of abdominal masses; after 2 wk. of therapy patient developed signs of vitamin B deficiency at angles of mouth; these cleared up in 1 wk.; patient died in uremia with uremic frost, 61 days after onset of therapy; had elevated urea nitrogen at onset of therapy
20 324	65 M	Metastatic carcinoma to subcutaneous tissue, Grade 1, site ? (anaplastic)	Biopsy of subcutaneous mass	250	1,250	5 days	Poor; large mass, subcutaneous, over right shoulder	No change; patient went downhill and died 6 days later
21 213	45 M	Carcinoma of rectum (adeno-carcinoma)	Biopsy of rectal tumor	1,000	128,000	128 days over 134 days	Fistula on buttocks; osteolytic lesions in pelvis; perianal tumor	No change in bone lesions on repeat x-rays; after 1 mo. fistula started healing (had chlortetracycline, too); after 2 mo. perianal mass grew slowly during therapy and patient changed to another form of therapy; died 246 days after therapy was begun
22 319	88 F	Carcinoma of breast	None	250	5,750	23 days	Very poor; debilitated; mass in left breast and enlarged left axillary nodes; bone metastasis	One wk. after onset of therapy some healing of ulcerated mass on breast was observed, but mass in breast seemed same size; patient went downhill and died 24 days later
23 302	38 M	Carcinoma of stomach (adeno-carcinoma)	Exploratory Laparotomy and biopsy of lymph node 1 yr. prior to therapy	500	12,500	25 days	Poor; large irregular epigastric mass; frequent vomiting	Patient continued to vomit and went downhill and died 28 days after therapy was begun; no change in epigastric mass
24 293	56 F	Carcinoma of cecum	Resection of tumor of ascending colon 19 mo. prior to therapy	750	9,750	13 days	Poor; subcutaneous metastasis, large liver	No essential change in condition; patient changed to another therapy and lost to study 28 days after onset of chemotherapy
25 248	37 F	Carcinoma of cervix (anaplastic)	Biopsy 3 days prior to therapy; no previous radiation	750	27,000	36 days over 40-day period	Fair; anemia; cervical tumor	No essential change in condition during puromycin therapy; after 40 days it was decided to transfer patient to radiation therapy; died 158 days after onset of puromycin therapy
26 297	57 F	Carcinoma of breast	Radical mastectomy 2 yr. 3 mo. prior to therapy; no radiation	250-500	22,500	45 days over 52-day period	Fever; general condition fair; enlarged left supraclavicular nodes; bone metastasis; lung metastasis; cough	After 1 wk. patient felt somewhat better; during 2d wk. patient started vomiting half hour after each puromycin dose; drug stopped; resumed 1 wk. later at 250 mg. daily and no vomiting; patient went progressively downhill and died 53 days after onset of therapy
27 283	63 M	Carcinoma of sigmoid (adeno-carcinoma)	Abdominal perineal resection 4 mo. prior to therapy	250-750	23,000	69 days	Mass around colostomy, left lower quadrant; general condition fair	After 3 wk. small decrease in size of mass in left lower quadrant around colostomy was observed; mass continued to slowly decrease; after 4 wk. of therapy patient complained of nausea and diarrhea; dose was decreased and nausea subsided; diarrhea continued; during therapy patient vomited occasionally; died 92 days after onset of therapy
28 308	44 M	Carcinoma of rectum (adeno-carcinoma)	Abdominal perineal resection 7 mo. prior to therapy	500	3,000	6 days	Hydronephrosis; partial intestinal obstruction; general condition poor	Patient under therapy 6 days; no change in condition; owing to drug shortage, medication discontinued; died 28 days after onset of therapy

TABLE 2.—*Summary of Clinical Results with Puromycin*—Continued

Case No. C. R. No.	Age and Sex	Diagnosis	Prior Therapy, Surgery, Radiation, Etc.	Puromycin: Daily Oral Dose, Mg.	Puromycin: Total Dose, Mg.	Puromycin: Total Duration of Therapy	Condition at Onset of Therapy	Clinical Response
29 296	42 F	Carcinoma of breast (Scirrhous)	Right radical mastectomy 4 yr. 9 mo. prior to therapy; no radiation	500	4,000	8 days over 12-day period	Paraplegia; bone metastasis	After 12 days patient developed maculopapular rash on face which she claimed was due to drug; refused further puromycin; lost to study
30 300	74 F	Carcinoma of cervix (squamous-cell carcinoma)	Radiation therapy ending 8 mo. prior to chemotherapy	250-500	52,250	113 days over 120-day period	Fair; cervical tumor	After 5th wk. of therapy, slight decrease in size of cervical tumor on pelvic examination; after 108 days of therapy, vagina admitted entire finger; surface of tumor nodular and less friable than before; formerly only a finger tip could be admitted; rectal mass less indurated and friable in uterosacral region has receded; lost to study after 121 days from onset of therapy
31 314	60 M	Carcinoma of prostate	Orchidectomy 5 yr. 11 mo. prior to puromycin; diethylstilbestrol for 5 wk., 5 yr. 10 mo. prior to puromycin	250-750	120,500	297 days over 326-day period	Bone metastasis; old orchidectomy; large hard prostate	Condition remained essentially the same under therapy for first 8 mo. of treatment; no changes in bone lesion on x-ray; after 8 mo. patient became weaker, bedridden, incontinent, developed spasms in thighs, and progressed downhill and died 326 days after onset of therapy; fluctuation of alkaline phosphatase but progressive decrease of acid phosphatase during therapy from 3.2 to 0 Shinowara units
32 312	.. F	Carcinoma of cervix (anaplastic)	Biopsy of cervical lesion	250-500	39,750	150 days	Carcinoma cervix; hydronephrosis; nephrostomy; vesicovaginal fistula; inguinal adenopathy	Condition remained essentially the same during therapy; 5 mo. after onset of therapy cervical tumor increased in size, remained ulcerated and friable; patient died suddenly, 177 days after therapy
33 276	68 F	Carcinoma of rectum (adenocarcinoma)	Biopsy of rectal tumor	250-750	101,500 to present	246 days to present	Hypertensive cardiovascular disease and arteriosclerosis cardiovascular disease; rectal mass	During first 9 mo. of therapy no apparent change took place in the size of rectal tumor; during the 10th mo. of therapy with puromycin, rectal mass grew larger and the patient was changed to another form of therapy; living 551 days to present
34 269	52 F	Carcinoma of breast (medullary carcinoma)	Right and left radical mastectomy, 2 and 5 mo. prior to puromycin; amethopterin for 5 mo. prior to puromycin	250-500	31,500	91 days	General condition fair; bilateral supraclavicular nodes; bilateral mastectomies; subcutaneous tumor masses; large fibroid	Five wk. after onset of puromycin therapy, subcutaneous tumor masses were larger; tumor masses continued to grow and patient changed to another form of therapy; died 1 yr. 5 mo. after onset of therapy
35 233	52 F	Carcinoma of breast (anaplastic carcinoma)	Biopsy of breast mass	5-1,000	67,895	312 days	Fair; large tumor left breast; bone metastasis; fibroid	After 1 mo. of puromycin, questionable decrease in size of left breast; 2 wk. later breast mass was softer in periphery; at this time patient complained of diarrhea (receiving 1 gm. daily); diarrhea continued and drug was decreased; diarrhea then subsided; after 7 wk. therapy, breast mass was smaller and softer; 1 wk. later bony lesions were noted on x-rays and diarrhea occurred (on 750 mg.) and drug was stopped; breast mass continued to get smaller and softer; 1 mo. later mass same size and patient changed to another form of therapy; 10 mo. later puromycin resumed; no significant improvement occurred and patient was changed to another form of therapy; lost to study after 604 days from onset of therapy

36 329	65 F	Carcinoma of breast (infiltrating duct-cell carcinoma)	Radical mastectomy 4 yr. 99 days prior to therapy; radiation therapy 4 yr. prior to therapy; testosterone for 5 mo. prior to puromycin	250	4,500	18 days	Very poor; large fungating right breast tumor; shortness of breath; pleural effusion; infiltration of right lung; large cervical and axillary glands; old left mastectomy	Patient went downhill and died after 19 days
37 241	49 M	Epidermoid carcinoma of skin (arising in area of bed sore)	Radical excision of lesion on buttocks 11½ mo. prior to therapy	250	2,250	9 days	Old hemiplegia; dilated aorta; large fungating nodes in right inguinal area; general condition very poor	No change in general condition; patient died after 10 days
38 323	.. M	Epidermoid carcinoma to nodes in left neck, Grade 1, site ?	None	250	8,000	32 days	Poor; emaciated, hoarse; large nodes left neck	Temporary slight decrease in size of nodes in left neck after 2 wk. of therapy; after 32 days of treatment, neck masses had increased in size and patient changed to another form of therapy; died 196 days after onset of therapy
39 298	58 M	Carcinoma of lung (adenocarcinoma)	Biopsy of subcutaneous tumor mass 3 days prior to therapy	250-500	42,500	120 days	Fair; lung infiltration; bone metastasis; large neck nodes; subcutaneous metastasis	One mo. after onset of therapy, slight decrease in size of nodes in neck and in shortness of breath; nodes then increased somewhat in size 2 mo. later and remained same size; patient gained weight under therapy; x-rays of lungs and bones showed no change in pathology until after 112 days of treatment, when lesions in lungs and area of rarefaction in scapula were larger; patient was changed to another form of chemotherapy; died 276 days after onset of therapy
40 295	72 F	Epidermoid carcinoma of mouth	None	250-500	21,250	61 days over 65 days	Poor; senile; large heart; masses in mouth on cheek and lip; node in left neck; emaciated; general arteriosclerosis	Ten days after onset of therapy tumor masses in mouth, lip, and cheek had decreased slightly in size; these masses continued to decrease in size during the 65 days patient was under study; during the first 31 days of study patient's general condition remained the same; patient then became drowsy and urea N increased; patient became comatose and died after 65 days
41 299	51 F	Carcinoma of breast (scirrhous)	Radiation therapy 13 mo. prior to therapy; radical mastectomy and rib section 11 mo. prior to therapy	750	47,250	63 days	General condition poor; ulcerations over entire right chest; liver 4 finger breaths below costal margin; fluid right chest, edema right arm; dyspnea	Six days after onset of puromycin therapy a decrease in dyspnea and cough occurred; during next month of therapy some apparent healing occurred in lesions on chest wall and decrease in size of liver occurred; patient died 64 days after onset of therapy
42 152	28 M	Hodgkin's disease	Biopsies of supraclavicular node; amethopterin for 4 mo., 3 yr. 3 mo. prior to therapy; triethylene melamine for 2 yr. and 9 mo., given 7 mo. prior to therapy; triethylene phosphoramide given for 7 mo. prior to puromycin	500-1,000	27,750	40 days	General condition fair; enlarged cervical nodes	No essential change occurred in size of enlarged nodes during 40 days of puromycin therapy; during the last 3 days of therapy patient complained of nausea 1-2 hr. after each dose of 250 mg.; medication was discontinued and 1 wk. later nodes appeared larger
43 338	77 M	Carcinoma of prostate (adenocarcinoma)	Suprapubic cystostomy and one-stage prostatectomy 7 yr. 5 mo. prior to therapy; bilateral orchidectomy 6 yr. prior to therapy	750	10,500	14 days	Poor; bone metastasis	No improvement; patient progressed downhill and died suddenly 15 days after onset of therapy

TABLE 2.—*Summary of Clinical Results with Puromycin*—Continued

Case No. C. R. No.	Age and Sex	Diagnosis	Prior Therapy, Surgery, Radiation, Etc.	Puromycin: Daily Oral Dose, Mg.	Puromycin: Total Dose, Mg.	Puromycin: Total Duration of Therapy	Condition at Onset of Therapy	Clinical Response
44 348	64 M	Carcinoma of prostate (adeno-carcinoma)	Transurethral prostatectomy 1 yr. 144 days prior to therapy; bilateral orchidectomy 1 yr. 109 days prior to therapy; diethylstilbesterol for 3 mo. ending 13 mo. prior to therapy	500-750	12,000	23 days	Bone metastasis; incontinent of urine and feces	General condition, x-rays, and laboratory studies remained unchanged during therapy; patient died suddenly 34 days after onset of therapy
45 313	73 F	Carcinoma of bladder (invasive papillary)	Biopsy of inguinal node and of bladder tumor; methopterin for 6 mo. prior to therapy	500-750	18,750	65 days	Fair; suprapubic tumor mass; edema of legs	One wk. after institution of puromycin therapy, patient complained of frequent nausea after medication; at onset of therapy patient had suprapubic mass extending 1 finger breadth below the umbilicus; 1 wk. after onset of therapy a definite marked reduction in the size of the suprapubic mass associated with a decrease in the peripheral edema of the legs occurred; suprapubic mass continued to grow smaller for 3 wk.; patient developed gross hematuria and urinary infection; suprapubic mass then increased in size and patient was placed on another form of therapy
46 343	40 F	Metastatic carcinoma Grade 1, site ?	Hysterectomy; biopsy	750	750	1 day	Poor; patient jaundiced; ascites; large liver	After 2d and 3d dose, patient vomited; patient changed to another form of therapy; died 20 days after therapy
47 214	25 F	Hodgkin's disease	Lymph node biopsies; triethylene phosphoramide for 5 mo. ending 2 mo. prior to puromycin; cortisone 2 wk. prior to and during puromycin therapy	250-750	6,250	21 days	Fair; generalized adenopathy; large hilar nodes	Patient started on 250 mg. puromycin 3 times daily; 1 day later started vomiting after each dose and the dose was reduced to 250 mg. daily; 17 days later patient complained of vomiting and drug stopped 2 days later; at this time the enlarged peripheral nodes were slightly smaller; patient changed to another form of therapy; died 126 days after therapy; through error received cortisone with puromycin therapy
48 368	33 M	Epidermoid carcinoma of skin	Biopsy	750	4,500	8 days	General condition at onset very poor; anemia; lesion over buttocks	Two days after onset of puromycin therapy patient developed loose stools; this condition continued; drug discontinued; diarrhea stopped 6 days after discontinuation of drug; patient changed to another form of therapy; no change in size or appearance of tumor during therapy
49 381	72 M	Carcinoma of mouth (squamous-cell)	Biopsy	750	750	1 day	Poor; pleural effusion; tumor of mouth; uremia	Patient died 1 day after onset of chemotherapy
50 398	74 F	Carcinoma of cervix (epidermoid)	Radium 1 yr. 3 mo. prior to therapy	750	4,500	6 days	Fair; large liver; suprapubic mass; peripheral edema; hematuria	No essential change in size of tumor or general condition; cystoscopy performed because of hematuria; 3 days later died suddenly
51 309	42 F	Carcinoma of breast	Biopsy of breast tumor	250-500	9,000	33 days over 47 days	Poor; breast tumors; bone lesions; lung lesions; epigastric mass; ascites	Patient progressed downhill and died 47 days after initiation of therapy

The puromycin was administered orally in dosages varying from 5 to 1000 mg. per day. The average daily dose provided was 250 to 750 mg. (given as 250 mg. once, twice, or thrice daily). The largest total dose was 128,000 mg., given to a patient with carcinoma of the rectum (Case 21). The drug was administered from 1 to 297 days in this series. The longest duration of puromycin therapy was in a patient with carcinoma of the prostate (Case 31). This patient received the drug daily for 297 days over a period of 326 days. In this series, 24 patients received puromycin for more than 30 days.

Table 2 presents a summary of results of the 51 patients with neoplastic diseases

TABLE 3.—*Results of Cases Treated with Puromycin*

Diagnosis	No. with Decrease in Tumor Size	No. Unimproved
Carcinoma of mouth	1	1
Carcinoma of esophagus	0	2
Carcinoma of stomach	0	2
Carcinoma of cecum	0	2
Carcinoma of sigmoid	2	1
Carcinoma of rectum	0	4
Carcinoma of anus	1	0
Carcinoma of gall bladder	0	1
Carcinoma of lung	1	2
Carcinoma of bladder	1	0
Carcinoma of prostate	1	5
Carcinoma of penis	1	0
Carcinoma of breast	3	8
Carcinoma of cervix	1	4
Carcinoma of skin	0	2
Metastatic carcinoma, primary site undetermined	1	2
Hodgkin's disease	1	1
Total	14	37

treated with puromycin. Slight temporary reductions in the size of tumor masses occurred in 14 of the patients in this series treated with puromycin. In 23 patients no essential change occurred in the size of tumor masses, and in 14 cases the tumor masses increased in size during puromycin therapy.

The diagnosis of the 14 cases in which slight decreases in tumor size occurred during puromycin therapy, listed in Table 3, were as follows: carcinoma of the mouth, 1 (Case 40); carcinoma of the sigmoid, 2 (Cases 19 and 27); carcinoma of the anus, 1 (Case 4); carcinoma of the lung, 1 (Case 39); carcinoma of the bladder, 1 (Case 45); carcinoma of the breast, 3 (Cases 22, 35, and 41); carcinoma of the prostate, 1 (Case 3); carcinoma of the cervix, 1 (Case 30); carcinoma of the penis, 1 (Case 10); metastatic carcinoma, primary site undetermined, 1 (Case 38), and Hodgkin's disease, 1 (Case 47). All but two of these patients received puromycin therapy for over 30 days. Two patients, one with carcinoma of the breast (Case 22) and one with Hodgkin's disease, received puromycin for 23 and 21 days, respectively. In general, these reductions in tumor size were of temporary duration.

The objective evidence of improvement and the type of case in which it was observed during puromycin therapy is as follows: 1. One patient with carcinoma of the mouth (Case 40) with associated generalized arteriosclerosis and dilation of the aorta, 72 years of age, showed a progressive decrease in size of the tumor masses in the mouth, in the left maxilla, and on the lower lip. This decrease in size was first noticed after 10 days of therapy and progressed slowly for the next 65 days she was under study. At this time the patient died in uremia. For two months prior to puromycin therapy, the patient was treated with a duodenal extract (WWDD) and oxytetracycline (Terramycin). On this therapy no essential change occurred in the size of the tumor masses. Oxytetracycline therapy continued with the administration of puromycin. Figures 2, 3, and 4 show the changes which occurred in the patient's lip tumor during puromycin therapy. 2. Two patients with carcinoma of the sigmoid showed changes. Case 19 showed a progressive decrease in the amount of ascites but no change in the size of the abdominal tumor masses during puromycin therapy. Case 27 showed a progressive reduction in the size of the large lower left quadrant mass—starting three weeks after initiation of therapy. Although the mass decreased in size, the patient went progressively downhill and died 92 days after onset of therapy. 3. In a patient with carcinoma of the anus (Case 4), with a large fungating mass in the left lower quadrant, a moderate reduction in the size of the mass occurred one month after institution of puromycin therapy. Two weeks later, how-

Fig. 2 (Case 40).—Patient with carcinoma of mouth 48 days prior to institution of puromycin therapy.

ever, the mass increased in size and the patient progressed downhill and died 58 days after institution of therapy. 4. One patient with carcinoma of the lung (Case 39) showed a slight decrease in the size of the enlarged cervical lymph nodes associated with a decrease in shortness of breath and weight gain one month after institution of puromycin

Fig. 3 (Case 40).—Same patient, showing reduction in size of tumor mass on lip 43 days after institution of puromycin therapy.

Fig. 4 (Case 40).—Same patient, showing further reduction in size of lip tumor 19 days later.

therapy. Two months later, however, the cervical nodes and bone metastasis increased in size and the patient was given another form of chemotherapy. Case 45, a 73-year-old woman with carcinoma of the bladder, had a marked reduction in the size of the suprapubic mass associated with a decrease in the

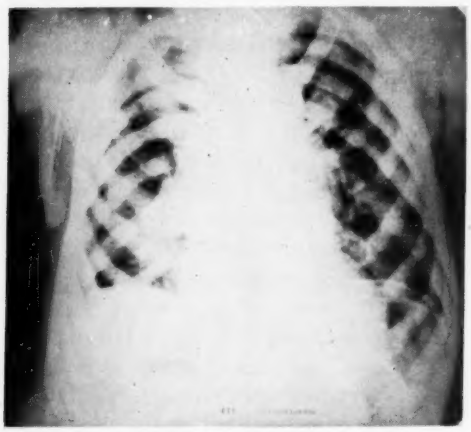
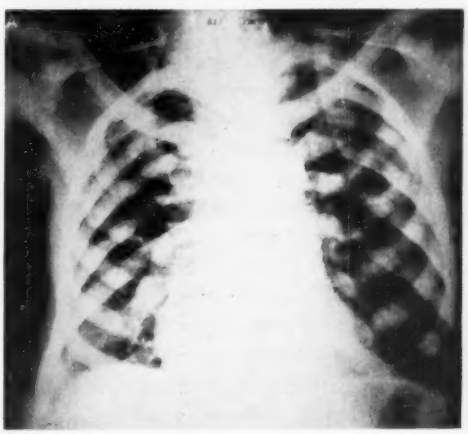


Fig. 5 (Case 3).—Roentgenogram of chest of patient with carcinoma of the prostate, taken 41 days after institution of puromycin therapy.

peripheral edema commencing three weeks after institution of puromycin therapy. This improvement continued for one week, at which time an acute urinary infection, hematuria, and an increase in peripheral edema and in the size of the abdominal mass in the right lower quadrant then occurred. The patient was subsequently changed to another form of therapy. Prior to puromycin therapy this patient had received amethopterin for six months. During the last month on amethopterin the patient's abdominal tumor masses increased in size. 6. Three patients with carcinoma of the breast showed changes under puromycin therapy. Case 22 showed some healing of the ulcerated breast mass one week after puromycin therapy had commenced, but there was no change in the size of the mass. Case 35, after one month on puromycin, showed some reduction in size and softening of the breast tumor. This continued for one month, but at this time new osteolytic bone lesions were observed. During the following month on puromycin no further change occurred in the size of the breast tumor, and the patient was placed on another form of chemotherapy. Case 41, a patient with pulmonary, liver, and skin metastases, showed some decrease in dyspnea and cough one week after institution of puromycin, and during the following month some slight healing occurred in ulcerated skin lesions over chest wall associated with a decrease in the size of the liver. With these changes, however, the patient progressed downhill and died 64 days after institution of therapy. In one patient with carcinoma of the prostate (Case 3), a slight decrease in the size of the right hilar mass of undetermined nature occurred after two months on puromycin therapy (Figs. 5 and 6). No other antibiotics were given to this patient during the interval of study. Repeated x-rays of bone lesions showed no change. A temporary increase, then decrease, occurred in both the alkaline and acid phosphatase during therapy. The general condition remained poor, and the patient progressed downhill and died 135 days after onset of therapy. One patient (Case 30) with carcinoma of the cervix showed some decrease in the size of the pelvic tumor mass after 108 days of therapy. Thirteen days later this patient was lost to study. 9. Case 10, a patient with carcinoma of the penis and hemiplegia, showed a definite decrease in the size of the penile lesion 17 days after onset of puromycin therapy. This lesion continued to decrease in size for 23 more days and then increased slightly. 10. Fourteen days after initiation of puromycin therapy in a patient with metastatic carcinoma, primary site undeter-

Fig. 6 (Case 3).—X-ray of chest of same patient, showing some reduction in size of right hilar masses 46 days later.



mined (Case 38), a reduction in the size of the enlarged lymph nodes in the neck occurred. Sixteen days later the masses in the neck had increased in size, and the patient was changed to another form of therapy. 11. One patient with Hodgkin's disease (Case 4) received cortisone 15 days prior to and during puromycin therapy. Hence it is not certain in this case which drug produced the decrease in size of the cervical nodes which occurred.

Table 4 shows the duration of illness prior to therapy according to the patient's history and the duration of illness prior to the patient's first hospital admission for the present illness. The duration between the first admission and establishment of a pathological diagnosis and the duration between the time of the histological diagnosis and chemotherapy with puromycin has been noted. The list also shows the surgery, radiation, and other chemotherapy administered to the patient prior to puromycin therapy, the time from the onset of therapy until death, the duration of chemotherapy, the duration of life after the pathological diagnosis had been established, and the present status of the patient.

While in some patients with disseminated carcinomatosis a temporary slight to moderate reduction in tumor size occurred, the patient's general progressive downhill course did not seem to be altered by the administration of puromycin. The reductions in the size of the tumor which did occur in these patients were generally not accompanied by a general clinical improvement in the patient. While an objective change was occasionally observed in some of the patients treated with puromycin, no subjective improvement was observed in any of these cases.

The clinical side-effects observed during puromycin therapy were nausea, vomiting, and diarrhea, which subsided promptly after discontinuance of therapy. These side-effects were seen in 12 of the 51 patients included in this series and occurred on dosages between 250 and 1000 mg. orally daily. The effects occurred from one day to one month following institution of therapy. Nausea occurred in two patients, vomiting in nine cases, and diarrhea in three cases. In two cases the diarrhea was associated with nausea or vomiting. The patients did not, apparently, develop tolerance to the drug. Once vomiting occurred it occurred following each capsule of 250 mg. In two cases, when therapy was resumed at a dose level of 250 mg. daily following subsidence of vomiting, vomiting occurred after each dose.

Repeat hemoglobin determination, red blood cell count, white blood cell count, platelet count, and differential blood count performed on 36 patients receiving puromycin showed no essential changes during therapy. In seven cases there was a progressive decrease in the hemoglobin and red blood cell count. In seven cases there was a slight increase in the hemoglobin and red blood cell count; five of these cases progressed downhill, and several had transfusions. One patient (Case 38), with metastatic carcinoma of undetermined primary site, had a decrease from normal in the white blood cell count to 4300 after 32 days on 250 mg. daily of puromycin. In one patient the white blood cell count fluctuated between 3050 and 9050 during therapy. In general, there does not seem to be any evidence from this study that puromycin affects the hemopoietic system.

Repeated urinalysis during therapy was performed on 23 of the cases studied and showed no essential changes when compared with urine specimens taken prior to therapy.

Blood urea nitrogen levels were determined at intervals during puromycin therapy in 35 cases. Increases in the blood urea nitrogen occurred in 12 of the 51 patients treated with puromycin (Cases 1, 4, 10, 16, 18, 19, 23, 26, 27, 40, and 50). Among the cases with uremia which did not come to autopsy several had complicating conditions which were likely to produce renal damage, independent of the administration of the drug. One patient with carcinoma of the penis (Case 10), who developed azotemia, had urethral stricture, hypertension, arteriosclerosis, albuminuria, and hemiplegia. A patient with carcinoma of the mouth (Case 40) who had nitrogen retention was 72 years old and had arteriosclerosis. Albumin and/or

TABLE 4.—*Survival Time of Patients Treated with Puromycin*

Case	Diagnosis	Duration of Illness Prior to Therapy (History)	Duration of Illness Prior to First Admission (History)	Duration Between First Admission and Pathological Diagnosis	Duration Between Diagnosis and Drug	Prior Therapy and Major Surgery	Time From Onset of Therapy Until Death	Duration of Drug Therapy	Duration Life After Diagnosis	Present Status
1	Ca. breast	6¼ mo.	1 mo.	4 days	4½ mo.	Radical mastectomy 4½ mo. prior to drug therapy	68 days	64 days	8 mo.	Dead
2	Ca. cecum	12½ mo.	8½ mo.	107 days	16 days	Exploratory laparotomy and partial resection left lobe of liver 16 days prior to drug therapy	135 days	18 days over 20 days	151 days	Dead
3	Ca. prostate	4 yr.	4 yr.	.....	4 yr.	Bilateral orchidectomy 4 yr. prior to drug therapy	142 days	111 days over 125 days	4½ yr.	Dead
4	Ca. anus	11 yr.	11 yr.	59 days	66 days	Abdominal-perineal resection 66 days prior to drug	58 days	57 days	124 days	Dead
5	Ca. rectum	8 mo	7 mo.	9 days	23 days	None	45 days	45 days	68 days	Dead
6	Ca. esophagus	3 mo.	2 wk.	15 days	2 mo.	Gastrostomy 16 days prior to drug	16 days	16 days	79 days	Dead
7	Ca. sigmoid	1 yr. 3 mo.	7 mo.	28 days	7 mo.	Resection of tumor of sigmoid 7 mo. prior to therapy	103 days	15 days over 21 days	9 mo.	Dead
8	Ca. breast	.....	.....	1 day	6 days	None	7 days	6 days	13 days	Dead
9	Ca. gall bladder	4 mo.; told of liver disease 12 yr. (?) previously	2 mo.	41 days	12 days	None	5 days	4 days	17 days	Dead
10	Ca. penis	6 mo.	3 mo.	1 day	92 days	Corticotropin for 77 days prior to puromycin	45 days	42 days	136 days	Dead
11	Ca. breast	1 yr.	. .....	.....	1 yr.	Right radical mastectomy 1 yr. prior to therapy; hysterectomy and oophorectomy 11 yr. prior to therapy	5 days	4 days	1 yr.	Dead
12	Ca. stomach	9 mo.	9 mo	2 days	6 days	None	51 days	42 days over 50 days	57 days	Dead
13	Ca. esophagus	4½ mo.	2 mo.	8 days	74 days	None	17 days	6 days	91 days	Dead
14	Ca. prostate	3 yr. 7 mo.	2 mo	40 days	3 yr. 4 mo.	Orchidectomy 3 yr. prior to therapy; prostatectomy 3 yr. prior to therapy; corticotropin 69 days prior to therapy	29 days	28 days	3 yr. 5 mo.	Dead
15	Ca. esophagus	10 mo.	4 mo.	88 days	97 days	None	4 days	3 days	101 days	Dead
16	Ca. cervix	1 yr. 9 mo.	1 yr.	1 day	274 days	None	29 days	26 days	303 days	Dead
17	Ca. lung	5 mo.	5 mo.	4 days	3 days	None	120 days	34 days	123 days	Dead
18	Ca. prostate	11 wk.	3 wk	9 days	49 days	None	23 days	22 days	72 days	Dead
19	Ca. sigmoid	2 yr. 3 mo.	6 mo.	16 days	1 yr. 9 mo.	Laparotomy and anterior resection	61 days	38 days over 69 days	1 yr. 11 mo.	Dead
20	Mestastatic ca., primary site ?	7 wk.	1 mo	19 days	2 days	None	6 days	5 days	8 days	Dead

TABLE 4.—*Survival Time of Patients Treated with Puromycin*—Continued

Case	Diagnosis	Duration of Illness Prior to Therapy (History)	Duration of Illness Prior to First Admission (History)	Duration Between First Admission and Pathological Diagnosis	Duration Between Diagnosis and Drug	Prior Therapy and Major Surgery	Time From Onset of Therapy Until Death	Duration of Drug Therapy	Duration Life After Diagnosis	Present Status
21	Ca. rectum	7 mo.	5 mo.	37 days	22 days	None	246 days	128 days over 134 days	268 days	Dead
22	Ca. breast	1 yr.	1 yr.	1 day	5 days	None	24 days	23 days	29 days	Dead
23	Ca. stomach	14 mo.	1 wk.	47 days	1 yr.	None	28 days	25 days	1 yr. 43 days	Dead
24	Ca. cecum	2½ yr	19 mo.	5 days	1 yr.	Resection of tumor of ascending colon 19 mo. prior to therapy; radiation prior to therapy	Lost to study after 28 days	13 days	Until lost to study 2 yr. 7 mo.	Lost to study
25	Ca. cervix	2 yr.	2 yr.	1 day	3 days	None	158 days	36 days over 40 days	161 days	Dead
26	Ca. breast	2 yr. 3½ mo.	1 wk.	1 day	2 yr. 3 mo.	Radical mastectomy 2 yr. 3 mo. prior to therapy	53 days	45 days over 52 days	2 yr. 5 mo.	Dead
27	Ca. sigmoid	1 yr. 9 mo.	1 yr.	25 days	4 mo.	Abdominal-perineal resection 4 mo. prior to therapy	92 days	69 days	1 yr.	Dead
28	Ca. rectum	15 mo.	9 mo.	6 days	7 mo.	Abdominal-perineal resection 7 mo. prior to therapy	28 days	6 days	8 mo.	Dead
29	Ca. breast	5 yr. 10 mo.	4 mo.	2 days	4 yr. 9 mo.	Radical mastectomy 4 yr. 9 mo. prior to therapy; no radiation	Lost to study after 88 days	8 days over 12 days	Lost to study	Lost to study
30	Ca. cervix	2 yr. 1 mo.	2 yr.	11 days	9 mo.	Radiation therapy ending 8 mo. prior to therapy	Lost to study after 121 days	113 days over 120 days	Lost to study	Lost to study
31	Ca. prostate	5 yr. 11 mo.	4 mo.	15 days	5 yr. 11 mo.	Bilateral orchidectomy 5 yr. 11 mo. prior to therapy; diethylstilbestrol for 5 wk., 5 yr. 10 mo. prior to therapy	326 days	297 days over 326 days	6 yr. 11 mo.	Dead
32	Ca. cervix	9 wk.	6 wk.	1 day	65 days	None	177 days	150 days	242 days	Dead
33	Ca. rectum	12½ mo.	6 mo.	7 days	6 mo.	Amethopterin for 6 mo. prior to puromycin	Living	246 days to present, 9/1/54	Living	Living
34	Ca. breast	11 mo.	3 mo.	20 days	5 mo.	No radiation therapy; left mastectomy 5 mo. prior to therapy; right mastectomy 2 mo. prior to therapy; amethopterin for 5 mo. prior to therapy	1 yr. 5 mo.	91 days	1 yr. 10 mo.	Dead
35	Ca. breast	9 mo.	8 mo.	12 days	1 day	None	Lost to study after 604 days	312 days	Lost to study after 604 days	Lost to study

36	Ca. breast	4 yr. 3½ mo.	5 wk.	1 day	4 yr. 99 days	Radical mastectomy 4 yr. 99 days prior to therapy; radiation 4 yr. prior to therapy; testosterone 5 mo. prior to therapy	19 days	18 days	4 yr. 119 days	Dead
37	Ca. skin	20 yr. ? (memory poor)	20 yr ?	13 days	1 yr. 2 mo.	Radical excision of lesion on buttocks 11½ mo. prior to therapy	10 days	9 days	1 yr. 66 days	Dead
38	Metastatic Ca., primary site ?	5 mo. 3 wk.	7 wk.	83 days	42 days	None	196 days	32 days	238 days	Dead
39	Ca. lung	2 yr. 1 mo.	2 yr.	3 days	3 days	None	8 mo.	120 days	276 days	Dead
40	Ca. mouth	12 wk	2 wk. ? (poor memory)	3 days	70 days	WWDD for 60 days prior to therapy	65 days	61 days over 65 days	135 days	Dead
41	Ca. breast	3 yr.	8 mo.	6 days	2 yr. 4 mo.	Radiation therapy 13 mo. prior to therapy; radical mastectomy 11 mo. prior to therapy	64 days	63 days	2 yr. 209 days	Dead
42	Hodgkin's disease	4 yr.	3 mo.	.....	4 yr.	Amethopterin for 4 mo., 3 yr. 3 mo. prior to therapy; triethylene melamine for 2 yr. 9 mo., 7 mo. prior to therapy; triethylene phosphoramide for 7 mo. prior to therapy	Living	40 days	Living	Living
43	Ca. prostate	11 yr. 5 mo.	4 yr.	7 days	7 yr. 5 mo.	Suprapubic cystostomy and one-stage prostatectomy 7 yr. 5 mo. prior to therapy; bilateral orchidectomy 6 yr. prior to therapy	15 days	14 days	7 yr. 5½ mo.	Dead
44	Ca. prostate	1 yr. 5 mo.	6 mo.	12 days	1 yr. 144 days	Transurethral prostatectomy 1 yr. 144 days prior to therapy; bilateral orchidectomy 1 yr. 109 days prior to therapy; diethylstilbesterol for 3 mo. ending 13 mo. prior to therapy	34 days	23 days	1 yr. 178 days	Dead
45	Ca. bladder	10 mo.	2 mo.	5 days	212 days	Amethopterin for 6 mo. prior to chemotherapy	208 days	65 days	1 yr. 55 days	Dead
46	Metastatic Ca., primary site ?	1 yr. ?	.....	.....	.....	Hysterectomy and biopsy	20 days	1 day	.....	Dead
47	Hodg'in's disease	2 yr. 9 mo.	17 mo.	50 days	3 yr. 2 mo.	Triethylene melamine, then triethylene phosphoramide for 2 yr. ending 2 mo. prior to therapy; cortisone 2 wk. prior to and during therapy	126 days	21 days	3 yr.	Dead
48	Epidermoid carcinoma of skin	5 yr. 11 mo.	5 yr.	28 days	10 mo.	Biopsy	37 days	3 days	11 mo.	Dead
49	Carcinoma of mouth	3 mo. 6 days	.....	1 day	1 yr. 4 mo.	Biopsy; radium	1 day	1 day	1 yr. 4 mo.	Dead
50	Ca. cervix	14 mo.	2 wk.	2 days	15½ mo.	Radium 15½ mo. prior to therapy	11 days	6 days	1 yr. 3½ mo.	Dead
51	Carcinoma of breast	6 mo	6 mo.	5 days	.....	Biopsy	47 days	33 days	42 days	Dead

gross blood was present in the urine prior to therapy in 8 of the 11 cases who developed azotemia. Six patients (Cases 4, 16, 18, 19, 27, and 50) prior to puromycin therapy had tumor masses in the pelvis which could account for mechanical urinary obstruction with impairment of renal function.

Repeated determinations of blood total proteins, sugar, albumin, icteric index, bilirubin, thymol turbidity, phosphorus, and alkaline phosphatase performed for 29 patients during puromycin therapy showed no essential changes. One patient (Case 3) with carcinoma of the prostate showed a temporary increase followed by decrease in both the alkaline and acid phosphatase. In Case 4, carcinoma of the anus, the alkaline phosphatase increased from 4.62 to 7.16 mg.; the total protein decreased from 8 to 5.06 gm., and the albumin decreased from 5.06 to 3.8 gm. The alkaline phosphatase increased from 1.44 to 10.56 mg. in the patient with carcinoma of the penis (Case 10). In Case 26, a patient with carcinoma of the breast, an increase in the level of the blood phosphorous from 5.51 to 7.58 mg. and in the alkaline phosphatase from 10.12 to 16.68 mg. occurred during puromycin therapy. In Case 31, carcinoma of the prostate, the alkaline phosphatase fluctuated during therapy, but the acid phosphatase decreased from 3.2 to 1.77 to 0 mg.

Autopsies were performed in 10 cases. In carcinoma of the breast, in one case (Case 1) there was a local recurrence of the tumor, with involvement of regional lymph nodes. In the remaining five cases (Cases 8, 11, 26, 34, and 51) metastatic lesions were found in one or more internal organs. Morphologically the metastatic tumors either resembled the original tumor tissue or showed a greater degree of metaplasia. In carcinoma of the digestive organs (Case 23, carcinoma of the stomach; Case 9, carcinoma of the gall bladder) there were extensive metastases. Squamous-cell carcinoma of the skin of the sacral region (Case 37), which for a long time remained well differentiated in repeated biopsies, became anaplastic and metastasized into the lung. Hodgkin's disease (Case 47) proceeded to sarcomatous transformation, with metastases to lungs, liver, and kidney. One patient (Case 26), who developed uremia, at autopsy proved to have obliteration of some glomeruli and ascending pyelonephritis (with clinical oxaluria), obviously not related to the administration of the drug. In another case with elevation of urea nitrogen (Case 23) the kidneys showed sclerosis of medium-sized and small arteries. The case of metastatic involvement of the kidney (Case 47) showed no disturbance of renal function. Of the remaining cases, none of which showed any clinical evidence of renal damage, six showed sclerosis of arteries and arterioles. A recent anemic infarct of the renal cortex was present in one of these cases (Case 34).

Slight vacuolization of epithelium in the distal convoluted tubules was seen in three cases, only one of which (Case 23) showed elevation of urea nitrogen. Since vacuolization was absent in the remaining seven cases, it is doubtful that it could be attributed to the drug.

Tissue culture investigations on the effect of puromycin on human tumors by Dr. Cobb indicated irreversible damage to cells at 40γ, 10γ, 4γ, and 2γ/ml. concentrations. There was a lack of preferential toxicity for specific cell types, and abnormal mitoses were not observed. Toxicity was manifested by bleb formation, cytolysis, and loss of staining ability. Stromal cells of multiple myeloma cultures exposed to 4γ/ml. of puromycin formed single giant vacuoles which enclosed eosinophilic material.[10]

SUMMARY AND CONCLUSIONS

Puromycin (Stylomycin), an antibiotic which shows appreciable inhibitory activity against a glioblastoma cultivated in the chick embryo, a mammary adenocarcinoma in the C3H mouse, and the mammary adenocarcinoma 755 of the C57BL mouse, was administered to 51 patients with advanced incurable disseminated neoplastic disease of varying types.

The average daily dose was from 250 to 750 mg. orally.

Temporary slight objective evidence of tumor regression occurred in 14 of the 51 patients. These patients received puromycin for 21 days or more. Their diagnoses were as follows: carcinoma of mouth, one; carcinoma of sigmoid, two; carcinoma of anus, one; carcinoma of lung, one; carcinoma of bladder, one; carcinoma of breast, three; carcinoma of prostate, one; carcinoma of cervix, one; carcinoma of penis, one; metastatic carcinoma, primary site undetermined, one.

While regressions in tumor size occurred in 14 patients treated with puromycin, there seemed to be no alteration in the patient's progressive downhill clinical course. The reduction in the size of the tumor was not accompanied by general clinical improvement in the patients treated.

The clinical toxicity of puromycin was shown by nausea, vomiting, and diarrhea which subsided promptly on discontinuation of therapy.

No definite changes in laboratory findings —complete blood cell count, blood urea nitrogen, alkaline phosphatase, phosphorus, sugar, total proteins, albumin, icteric index, bilirubin, or thymol turbidity—which could be accounted for by the therapy occurred.

Since puromycin shows some temporary inhibitory effect against certain human tumors, the testing of its chemical breakdown products in human neoplasms is warranted.

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Treatment in Internal Medicine

MANAGEMENT OF MASSIVE GASTROINTESTINAL HEMORRHAGE ON THE WARDS OF THE BOSTON CITY HOSPITAL

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THE SUCCESSFUL management of patients with massive upper gastrointestinal hemorrhage requires knowledge of the pathology of lesions responsible for bleeding and familiarity with the available methods for their prompt recognition. In addition, understanding of the physiology of the bleeding state, affected as it is by age, rate of bleeding, and concomitant diseases, is necessary for continuous assessment of the patient's condition. These and other factors determine the choice of therapy, and, in particular, the timing of surgical intervention.

The problem of management is particularly challenging on the wards of a large municipal hospital, where patients often arrive in an advanced stage of illness. The experience of many physicians who have studied this problem on the wards of the Boston City Hospital has emphasized the value of a working plan of management. The following discussion comprises one such broad outline which has proved practicable. Since patients with this syndrome are routinely admitted to the medical wards, this protocol is prepared especially for the guidance of the newly arrived medical house officer.

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DEFINITION AND RECOGNITION OF MASSIVE UPPER GASTROINTESTINAL HEMORRHAGE

Massive upper gastrointestinal hemorrhage may be defined as consisting of gross hematemesis and/or tarry or grossly bloody stools, sufficiently severe to require transfusion. It is often accompanied by shock of varying severity. Although it is usually clinically obvious, it is not always clinically recognized. Hematemesis is sometimes erroneously reported as hemoptysis. In 29% of 101 autopsied patients with fatal gastrointestinal hemorrhage, bleeding was unrecognized at the time of admission work-up.[1] In some patients the admission diagnosis of myocardial infarction or cerebral thrombosis was, in fact, secondary to the unrecognized intestinal hemorrhage.[2] The hemorrhage terminated the illness of 31 patients hospitalized for unrelated disease, such as congestive heart failure, cerebral vascular disease, pneumonia, or malignant disease, the hemorrhage occurring for the first time after admission. In 24 patients the presence of hemorrhage was clinically unsuspected until autopsy. This incidence may be reduced by routine observation of all stools by nurses, attendants, and physicians. In instances in which painful digital examination of the rectum is considered unduly hazardous, as, for example, in patients with recent myocardial infarction, the careful insertion of a rectal swab may be substituted. The possibility of massive hemorrhage must be considered in every patient admitted with an unexplained anemia and in every patient who suddenly takes an unexplained turn for the worse on the hospital wards.

IMMEDIATE MANAGEMENT OF THE PATIENT ADMITTED TO THE HOSPITAL WITH OVERT UPPER GASTROINTESTINAL HEMORRHAGE

Treatment of Shock.—A saline intravenous infusion should be started at once

through a large-gauge (No. 18) needle. Failure to do so may cause undue delay in needling collapsed veins should severe shock supervene. Blood is drawn for routine hematological studies, typing, and cross matching. In the presence of shock, exhaustive history-taking and physical examination should await initiation of fluid replacement. The patient usually gives evidence of shock in pallor, sweating, thirst, and elevation of pulse prior to fall in blood pressure. Coma is a rare manifestation of hemorrhagic shock. Cyanosis in the presence of shock is often a clue to the presence of cardiopulmonary disease. The normal physiologic mechanisms usually accomplish maximal vasoconstriction without the use of vasopressor drugs. Intravenous arterenol (Norepinephrine), however, may be useful as a temporary measure while fluid replacement is being sought or when shock fails to respond to other methods. Screening for severe liver disease is accomplished by the injection of 5 mg. of sulfobromophthalein (Bromsulphalein) dye per kilogram of body weight into the initial saline infusion tubing and the determination 45 minutes later of the amount retained in the blood.[3]

Fluid replacement should be continued until rehydration is manifested by elimination of thirst, moistening of the tongue, and adequate output of urine with low specific gravity. Blood is replaced as promptly as is commensurate with blood loss and maintenance of cardiopulmonary integrity. While blood is being sought or when adequate supplies are not available, plasma expanders, gelatin solutions, and other blood substitutes should be utilized. The prompt return of the hematocrit level to a value of at least 30% provides the patient with a margin of safety in case of renewed bleeding, while vigorous diagnostic studies are being performed.

Since patients requiring emergency surgery must be identified promptly, accurate early diagnosis of the cause of bleeding is essential. Accordingly, at this time, as complete a history and physical examination must be performed as is commensurate with making such a diagnosis. The diagnostic importance of the presence or absence of abdominal masses, liver, spleen, and ascites warrants definitive abdominal examination. Diagnosis based on clinical findings alone is not sufficiently reliable in many instances.

Patients bleeding from varices secondary to cirrhosis of the liver may manifest none of the hepatic stigmata. Similarly, definite symptoms of peptic ulcer or gastric neoplasm are often wanting. Furthermore, multiple lesions are not uncommon, and Palmer and Brick found that 39% of their patients with gastrointestinal hemorrhage and demonstrable esophageal varices had one or more other lesions of the upper gastrointestinal tract which could have caused bleeding.[4]

For these and other reasons, the use of diagnostic adjuncts is widely practiced at the Boston City Hospital.[5]

Early Roentgen Examination.—The most useful of these is emergency roentgen examination.* This is routinely scheduled for the morning after admission, but it may be performed earlier when indicated. All food and oral medication are omitted for a period of 8 to 12 hours prior to the x-ray study. Examination may be postponed because of active bleeding or definite shock or when patients are unable to cooperate. When delayed, the procedure is rescheduled for the following morning. Certain patients with uncontrolled massive hemorrhage may be sent to surgery without benefit of emergency x-ray diagnosis when the risk of delaying surgery is greater than the advantage to be gained by identifying the site of bleeding. The completeness of the roentgen examination depends on the patient's condition as determined by the radiologist and the patient's physician. The more complete the examination performed, including the application of pressure and the use of the standing position, the more accurate the diagnosis. It has been found that patients tolerate the standing position better shortly after hospitalization than they do after a week or so of bed rest.

* References 6 and 7.

Early roentgen examination is most reliable in the identification of peptic ulceration, less reliable in the diagnosis of esophageal varices, and least useful in the diagnosis of hemorrhagic gastritis. Blood clots rarely comprise a serious limitation. Close cooperation between the patient's physician and the radiologist is essential. An accurate clinical diagnosis will often direct the radiologist's attention to the most likely site of bleeding and help to pinpoint small lesions easily overlooked on routine roentgen survey. The use of early roentgen examination reduces the number of patients with undiagnosed bleeding sites.[8] Small peptic ulcerations are found which, because they heal promptly, would not be visualized on later roentgen examination. When the patient's condition is unstable, he should be accompanied by his physician, and the radiologist may limit his examination. If the initial examination is negative or equivocal, repeat examination should be performed as soon as the patient's condition permits.

Although emergency roentgen examination is not without danger, its judicious use at this hospital is clearly warranted. The accurate localization of the bleeding site expedites the decision regarding operation and aids in determining the risk of surgery. The elimination of the need for time-consuming exploratory procedures further reduces the surgical risk.

EARLY DIAGNOSIS OF ESOPHAGEAL VARICES

In the absence of jaundice, the clinical recognition of liver disease severe enough to cause varices is not always possible. Emptied of blood, capillary telangiectases and collateral abdominal veins may be invisible and spleens may shrink in size. A normal retention of sulfobromophthalein (5% or less) or only slight elevation, is usually found in patients without liver disease in spite of shock, advanced age, or fever. A retention of 15% or greater is regularly found in patients with severe liver disease, and a persistently high retention lasting usually several days is characteristic of patients with advanced cirrhosis. Liver disease of lesser severity, for example, fatty liver, cholangitis, and minimal or early cirrhosis, may also be accompanied by an initially high retention. This, however, usually falls promptly, sometimes as early as 12 hours after the initial test. It should be remembered that the above results are those obtained during acute bleeding or shortly after admission to the ward for acute bleeding. Congestive failure, pneumonia, and other infections may also be associated with reversible elevation of sulfobromophthalein retention. A normal sulfobromophthalein test excludes the possibility of esophageal varices secondary to cirrhosis; a high sulfobromophthalein retention, on the other hand, indicates the need for further study. Esophageal varices secondary to extrahepatic portal obstruction (Banti's syndrome) are not distinguished by the test in the absence of cirrhosis. Clinical recognition of this condition must be relied on (youth, splenomegaly, etc,). The finding of a normal or only slightly elevated sulfobromophthalein retention is most helpful in a patient with fulminant hemorrhage from an undiagnosed site, since it permits emergency surgery to be performed by excluding the possibility of varices secondary to advanced cirrhosis.

E. E., a 49-year-old man, was admitted to the hospital after having had rapid hematemesis for 18 hours. On admission to the hospital he was in profound shock and produced liquid bloody melena in addition to bloody vomitus. He admitted to being a chronic alcoholic for 20 years. Although no stigmata of cirrhosis were apparent, the admission diagnosis was bleeding esophageal varices. A sulfobromophthalein retention of 6% contraindicated this diagnosis. The patient was too ill for x-ray study and was transferred to the operating room, where emergency surgery was performed four hours after admission. A large lesser-curvature gastric ulcer was removed.

Although roentgen demonstration of esophageal varices in cooperative nonbleeding patients is usually successful, patients with active recent hemorrhage may be too ill for transfer to the x-ray examination room or for complete roentgen examination of the esophagus. In such instances, emer-

gency esophagoscopy has proved to be the diagnostic procedure of choice.

Esophagoscopy.—This procedure has the advantage that it can be performed at the patient's bedside.[9] The experience at this hospital has confirmed the reports of others emphasizing the superiority of this method for establishing the diagnosis of bleeding esophageal varices.† In spite of the advanced age and severe illness of some patients, relatively little discomfort has been encountered, and no deaths and no serious complications have been attributed to the procedure. One cannot overemphasize, however, that esophagoscopy is potentially dangerous and requires experienced workers with trained assistants. Bedside examination should be discontinued if the patient fails to cooperate. Esophagoscopy is the only nonoperative method for the direct visualization of esophageal varices. Only by such direct visualization can it be ascertained that bleeding derives from varices rather than from a coexisting lesion, such as gastritis or peptic ulcer. When bleeding varices are found, oxidized cellulose, U. S. P. (Oxycell) gauze (absorbable hemostatic) may be introduced through the esophagoscope with the aim of promoting clot formation, or esophageal balloon tamponade may be employed.

Esophageal Balloon.—When esophagoscopy is not possible, an esophageal balloon may be useful in supporting the clinical impression of bleeding esophageal varices.[12] The prompt cessation of bleeding on introduction and inflation of the balloon and the resumption of bleeding on deflation permits a presumptive diagnosis of esophageal varices. The use of the esophageal balloon enables diagnostic discrimination between multiple lesions of the upper gastrointestinal tract. In several of our patients coexisting esophageal varices and duodenal ulcers were diagnosed. The correct site of bleeding was indicated by appropriate observations made with the tubes in place. A triple-lumen tube attached to a single gastric balloon has been used as a diagnostic aid.[13]

Gastroscopy.—Although emergency gastroscopy has not been widely used at the Boston City Hospital, its successful use in other clinics clearly warrants its wider application.‡ It is especially useful in the diagnosis of gastritis, superficial peptic ulcerations, lacerations of the mucosa of the cardioesophageal junction,[15] gastric polyps, and gastric artery aneurysms,[16] all lesions which may be difficult or impossible to diagnose by roentgen examination. It is our practice to request emergency roentgen examination prior to gastroscopy. Patients with acute gastritis tolerate the procedure poorly, and it is usually necessary to delay the examination for several days. Undue delay, however, may prevent establishment of diagnosis because of the reversibility of the diffuse gastric lesions.

Hemorrhagic Diatheses.—The above procedures supplement the routine history and physical and laboratory examinations by which medical causes of bleeding may be recognized. Generalized bleeding tendencies, as in drug intoxication, thrombocytopenia, uremia, and diseases of the spleen and bone marrow, are responsible for relatively few cases of massive gastrointestinal hemorrhage. When such a tendency does occur, clinical evidence of bleeding elsewhere usually accompanies the digestive tract bleeding.

Severe liver disease, however, is regularly accompanied by coagulation defects, thrombocytopenia, and increased capillary fragility, which may contribute to bleeding from varices, ulcers, or gastritis in cirrhotic patients.§ These may be severe enough to be associated with clinical evidence of generalized bleeding defect, i. e., purpura, diffuse petechiae, or multiple bleeding sites, or be manifested only by laboratory abnormality.

Simple screening laboratory procedures are usually sufficient to reveal the blood

† References 10 and 11.

‡ References 11 and 14.

§ References 17-19.

dyscrasia; examination of stained smear for thrombocytes, determination of bleeding and clotting times, tourniquet test, and one-stage prothrombin determination will identify most cases.

CLOSE PATIENT FOLLOW-UP

Success in management of this syndrome is dependent upon close observation of all patients, including those who give no overt evidence of continued bleeding. Patients rarely, if ever, die from severe gastrointestinal hemorrhage without giving some clinical forewarning of internal bleeding. Characteristic symptoms, such as weakness, chilliness, giddiness, faintness, syncope, nausea, vomiting, increased bowel activity, skin pallor, and thirst, as well as changes in pulse and blood pressure, occur almost invariably. These signs, however minimal, should alert the physician to the possibility of renewed bleeding. Failure to check the patient over a period of several hours may prove catastrophic. When the physician's attention is diverted by other duties, he may delegate the responsibility of checking the patient to other physicians, nurses, ward attendants, and medical students. On busy wards where nursing attendants are limited, the patient's bed should be moved to a point as close as possible to the nurse's desk, where she can observe the patient while carrying out her other duties. When the physician leaves the ward at the end of the day, he should review the patient's status with the relieving physician and nursing personnel responsible for the night care.

In addition to the above signs, a careful record of the volume and character of the patient's urine, stool, and vomitus should be carefully recorded on a bedside chart. The advantage of an inlying bladder catheter must be weighed against the danger of possible genitourinary tract infection. The accompanying figure shows one variety of bedside chart which has proved useful in assuring close follow-up of our patients.

The best evidence for active bleeding is, of course, the direct observation of liquid blood vomited or passed by rectum. Laboratory tests are not necessary to establish the desperate state of the patient who continually vomits blood or produces liquid melena in large quantity. Most patients, however, do not bleed so severely, and one must rely on the clinical and laboratory findings. In addition to the clinical and physiologic observations noted above, repeat blood hematocrit observations are particularly useful. Although the initial hematocrit value does not exactly reflect the degree of recent severe blood loss, the change in hematocrit level following adequate hydration is a more reliable index of bleeding. In the average patient approximately a three-unit rise in the hematocrit value results from each 500 cc. of blood given. Failure to effect this rise with each transfusion suggests either inadequate hydration or continued bleeding. The finding of hypochromic red blood cells on admission suggests chronic blood loss in addition to the acute bleeding. Since the normal kidney adjusts immediately to alterations in blood volume, frequent observations of the volume and specific gravity of the urine give prompt clues to changes in this volume. Much has been written on the value of "blood volume" measurements as an index of the amount of bleeding.[20] While such tests are undoubtedly helpful, they are not entirely necessary and by diverting attention from the patient himself may sometimes be more harmful than beneficial.

SELECTION OF PATIENTS FOR EMERGENCY SURGERY

This difficult decision can be made only by weighing the numerous factors which determine the relative risks of medical and surgical therapy. These vary from patient to patient and in the same patient at different times. The single-minded attitude of extremists, surgical or medical, simplifies the decision only by ignoring the complexity of the problem.

These factors must be considered:

1. The site and nature of the bleeding lesion. Peptic ulcerations of the distal portions of the stomach or of the duodenal cap are more amenable to surgical therapy than are lesions elsewhere in the stomach, duo-

BOSTON CITY HOSPITAL

GASTRO-INTESTINAL HEMORRHAGE

PROGRESS CHART

Name | Age | Service | Hosp. Number

Date

A.M. or P.M.

Hour: 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12

Pulse • — B.P. S ! D • — Hematocrit

260 160 150 140 130 120 110 100 90 80 70 60 50 — 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 — 55 50 45 40 35 30 25 20 15 10

Blood
Date Donated
Transf. No.
Saline
G. in W.
Other
Hematemesis
Melena
Clin. Signs of Shock
Oral Food { Type / Amt.
Output — Urine
Tube
Vomitus (no blood)
Esophageal Tube
Diagnostic Procedures and Comment

Progress chart used in management of gastrointestinal hemorrhage.

denum, or esophagus. Posterior wall ulcers may be difficult to dissect from the underlying pancreas. Diffuse hemorrhagic gastritis may require total gastrectomy, if any surgical procedure at all is contemplated. Scarring from previous upper abdominal surgery may increase considerably the difficulty of gastric resection. The high morbidity and mortality of emergency surgical intervention in bleeding esophageal varices argues strongly for nonoperative therapy. (See below.)

2. Rate of bleeding. There is general agreement that the rate of bleeding largely determines intervention in operable lesions, such as benign peptic ulceration. Most patients with massive gastrointestinal hemorrhage have stopped bleeding before or shortly after admission to the hospital. These patients respond satisfactorily to medical therapy and present no problem.

A very small percentage of patients bleed so massively when first seen that immediate exploratory laparotomy may be necessary to save life, despite advanced age, medical complications, and other unfavorable circumstances. Medically uncontrollable bleeding in these patients is obvious by continuous hematemesis or liquid bloody stools and falling hematocrit value despite abundant transfusion. Emergency roentgen examination is usually not feasible. Bleeding esophageal varices may be excluded by the use of the sulfobromophthalein retention test and, when indicated, emergency esophagoscopy. Although the surgical mortality is great, the risk of not operating is clearly greater. Surgery must be undertaken as soon as the operating team can be assembled.

There remains a third group of patients who manifest intermittent or continuous bleeding of lesser severity by the passage of tarry stools or, less frequently, hematemesis. Some may require transfusion of a unit or more of blood daily to maintain a stable hematocrit value. Because fulminant hemorrhage will supervene in some of these patients, considerable controversy revolves about the use of emergency surgical intervention. Since the bleeding in most of these patients will subside under conservative management, the routine use of emergency surgery is clearly unwarranted. Dunphy and associates have attempted to simplify the decision by setting an arbitrary limit to the rate of bleeding tolerable without surgical intervention: namely, failure to maintain stable circulation and hematocrit levels despite transfusions amounting to 500 cc. every eight hours.‖

Rational selection dictates consideration of many other factors in addition to the rate of bleeding.

3. Adequacy of and response to therapy. When evidence of bleeding persists or begins to worsen, despite intensive medical therapy, emergency surgery may be warranted even when bleeding is not massive in order to avoid the risk of subsequent uncontrolled bleeding. The persistence of ulcer pain adds support to this early decision for surgery. The duration of the therapeutic trial varies from patient to patient and is itself dependent upon other factors. The presence of obstruction, penetration, or perforation of a peptic ulcer may precipitate the decision for surgery. Assessment of any patient with continued bleeding must be made at finite intervals. The decision to procrastinate is never for an indefinite period of time. The length of the interval is determined by the urgency of the patient's condition.

4. Advanced age and complicating medical disease. A common oversimplification is that advanced age makes emergency surgery mandatory in patients with massive gastrointestinal hemorrhage. Clearly, the risk of surgery is increased by advanced age, as well as by coexisting disease of the liver, lungs, heart, and kidneys. A moderate rate of bleeding, on the other hand, readily controlled by blood replacement, may not significantly endanger the patient's life. Yonemoto, Vigneron, and Osborne ¶ have pointed out that a high percentage of surgical fatalities occur in patients with unsuspected

‖ References 21 and 22.

¶ Yonemoto, R.; Vigneron, M., and Osborne, M. P.: Unpublished data.

complicating disease. They emphasize the importance of complete medical evaluation of the patient prior to surgical intervention. In addition to routine physical and laboratory studies which disclose the presence of congestive failure or renal disease, the sulfobromophthalein test is recommended as a screening test for liver malfunction, and electrocardiography, for acute cardiac disorders. Although elevations of blood NPN commonly occur in massive intestinal bleeding, unduly elevated or persistently high levels warn of underlying renal disease, especially when accompanied by urine of low specific gravity.

Precise assessment of the elderly patient with his concomitant medical complications cannot be replaced by "rules of thumb." [23] Prompt recognition and treatment of congestive failure, pulmonary infection, diabetes, and other medical complications lowers the mortality of massive hemorrhage. Because one cannot accurately predict the onset of increased bleeding, this complete work-up must be performed as promptly as possible on all patients.

Much can be done for the alcoholic patient, who usually arrives at the hospital in a badly depleted nutritional state. Liver repair, which may begin promptly on cessation of alcohol intake, is facilitated by replacement of nutrients, both by mouth and by vein, and is reflected in reduction of liver fat with secondary diminution of portal venous pressure and improved liver function and blood coagulation. In these patients, delay of surgery may be indicated when possible.

5. Team factors. The best management of all patients with massive gastrointestinal hemorrhage demands close teamwork.[24] The skill and experience of the operating team dictates to some extent the selection of patients for surgery. In complicated cases the consulting surgeon can best assess his own talents and those of his assistants, the anesthesiologist, house physicians, and nurses who will provide surgical and postoperative management. In some instances he may delay surgery until optimal operating arrangements can be made, or, on the other hand, he may decide for immediate surgery to take advantage of ideal arrangements. Frequent meetings and free discussion between medical and surgical physicians expedite clearer understanding. An honest appraisal of the limitations of the available facilities, including blood bank, laboratory services, nursing care, roentgen diagnosis, etc., is necessary for proper application of surgical therapy. Thus, it may be reasonable to decide in favor of medical therapy in a patient with advanced renal disease if laboratory facilities are unavailable for the extensive electrolyte determinations required for best postoperative management.

GENERAL CONSIDERATIONS OF MEDICAL MANAGEMENT

1. Sedation. Contrary to common practice, morphine is not good therapy for medical shock. Sedative drugs, usually barbiturates, are reserved for those patients who manifest undue anxiety. Patients with massive gastrointestinal hemorrhage are most effectively reassured by the confident manner with which the attending physician demonstrates his control of the situation. Sedation must be used sparingly in patients with advanced liver disease, since hemorrhage may precipitate hepatic coma. Many patients pass through a hyperactive, agitated phase before they become stuporous, and the unwary intern may prolong coma by the injudicious use of excess quantities of sedative drugs. Pain is usually not a troublesome problem in patients with peptic ulcer and hemorrhage and is treated better by food, antispasmodics, and antacids than by narcotics, which may obscure their diagnostic and therapeutic effect.

2. Feeding and antacid therapy. Food may be given as tolerated. Patients with gastritis often will not tolerate even water by mouth. It is sound practice to treat all gastrointestinal bleeding as arising from a peptic ulcer until proved otherwise, since the peptic acid factor may contribute to bleeding from other lesions such as esophageal varices, gastritis, and gastric cancer.

The late Franklin W. White # preferred the use of gruel (a thin mixture of cooked cereal and skimmed milk or water) to a milk and cream regimen, because the curds formed by the latter delayed gastric emptying and interfered with roentgen study, Because he considered milk a severe irritant to the peritoneal cavity, he withheld milk feeding as long as surgical intervention was a possibility. Many useful "antacid" preparations are available alone or in combination with gels or magnesium salts and may be alternated with food. High-protein foods actually comprise the most effective acid neutralizers. Therapy should be given on a 24-hour basis until all evidence of bleeding has subsided. Antivagal therapy may be provided in the form of atropine, tincture of belladonna, or one of the several proprietary preparations. Vomiting dictates the use of parenteral preparations. They should be discontinued, however, for a period of at least four hours prior to scheduled gastrointestinal roentgen examinations, because an atonic stomach cannot be satisfactorily studied. The use of chlorpromazine parenterally provides effective treatment for excessive vomiting. Immoderate use, however, may obscure continued bleeding and worsen rather than improve prognosis. Constipation is a common complication of this ulcer regimen. The addition of barium for roentgen study may cause fecal impaction. For this reason in elderly patients the regimen must be modified, and smaller quantities of milk, antacid preparations, and antivagal drugs should be administered.

3. Gastric intubation. The judicious use of the gastric tube may help to localize bleeding above or below the pylorus. Renewed bleeding from gastric or esophageal lesions may be promptly recognized by aspiration of blood. The demonstration of the presence or absence of free hydrochloric acid not only provides diagnostic information but also supports or contradicts the use of vigorous antacid therapy. Palmer suggests that the introduction of ice water through the tube may help to stop bleeding from gastritis. While the introduction of a gastric tube in a patient with esophageal varices may not be desirable, the benefit to be gained by the use of a soft tube in a patient who tolerates it well far outweighs its possible risk.

4. The early management of hemorrhage from esophageal varices. Immediate direct efforts may be taken to occlude or to shunt the blood away from the bleeding varices. Indirect medical efforts are made to improve the liver function and blood coagulation and to reduce the portal pressure.

(*a*) Direct efforts to occlude or shunt the bleeding varices. Esophageal tamponade by direct packing with thrombin preparations through the esophagoscope has been used with success in a limited number of cases in this hospital.* Esophageal balloons provide a more effective method for applying pressure on the esophageal veins. There are several types of these balloons. The Sengstaken tube applies pressure not only on the esophagus but also on the adjacent gastric cardia by means of a gastric balloon.[12] In the absence of a double balloon, a single gastric balloon many be pulled tightly against the cardioesophageal junction.[13] In my opinion, the use of esophageal balloon tamponade is the treatment of choice for bleeding esophageal varices. The tube is difficult to introduce, however, and troublesome to maintain. Constant supervision by intelligent attendants is essential. Atropine may be used to reduce oral secretions, and esophageal suction may be necessary to prevent aspiration. The tubes must be checked regularly to insure inflation of the balloon. Introduction of liquids into the wrong lumen complicates withdrawal of the tube. The balloons may be deflated at regular intervals without removing the tube to ascertain whether bleeding has subsided. Even in the absence of renewed bleeding the

Dr. White stimulated and supervised renewed study of this problem at the Boston City Hospital. White, F. W., and Chalmers, T. C.: The Problem of Gross Hematemesis In A General Hospital, *Tr. A. Am. Physicians* **61**:253, 1948.

* References 9 and 10.

tube should not be removed for several days, since bleeding may recur and reintubation is often more difficult than the initial intubation.

Unsatisfactory as the procedure may be, it is much to be preferred in the usual case to direct surgical attack, which is attended by a high mortality in the nutritionally depleted alcoholic cirrhotic patient. While bleeding is being controlled by tubal methods, vigorous medical therapy can do much for the patient during the first few days of hospitalization.

(*b*) Medical management of acute hemorrhage from esophageal varices. The use of vigorous nutritional supplementation by mouth, gastric tube, or vein may aid in the prompt elimination of fat from the liver of the alcoholic patient, thus reducing intrahepatic pressure and, secondarily, portal vein pressure. Protein and lipotrophic substances such as methionine and choline are recommended. Supplementary amino acid solutions may be utilized. Characteristic flapping tremor of the hands and hyperexcitability presaging hepatic stupor may necessitate reduction of protein intake.† The development of ascites and edema calls for immediate sodium restriction.

Alcoholic patients are usually deficient in many vitamins. Vitamins of the B group and folic acid supplementation may be provided by the use of parenteral crude liver extract. Some patients have frank scurvy; almost all are deficient in vitamin C. Replacement of this vitamin in large quantity, e. g., as much as 1 gm. daily, is indicated routinely. Prothrombin deficiency resulting from inadequate intake or absorption of vitamin K may be quickly reversed by use of parenteral supplementation. Some patients with hepatic cirrhosis and bleeding varices manifest markedly reduced platelet levels. The use of fresh blood transfusion may be warranted in such circumstances. Complicating pulmonary infection should be treated by appropriate antibiotics.

† References 25 and 26.

The combined use of esophageal balloon tamponade and vigorous medical therapy will control bleeding in many cases. Several days of medical therapy will put the patient in better condition for definitive shunt surgery if it is indicated, and, equally important, provide the opportunity for judicious selection of candidates for this procedure. The management of ruptured varices in the patient with known postnecrotic cirrhosis (postinfectious hepatitic cirrhosis or healed acute yellow atrophy) may be different from that of the patient with alcoholic or fatty nutritional cirrhosis. Because he has little or no fat in his liver and fewer medical complications, protracted medical therapy has less to offer. Balloon tamponade may be utilized as an emergency measure, and the decision for shunt surgery may be made sooner. The place of surgery, emergency or elective, in the management of massive hemorrhage from esophageal varices is being actively investigated in many clinics and should be considerably clarified in the near future. The great need for proper control observations in assessing the results of surgical therapy has recently been emphasized.[27]

5. Early management of hemorrhagic gastritis. Diffuse gastritis is not sufficiently widely recognized as an important cause of massive upper gastrointestinal hemorrhage. It may coexist with other lesions of the upper intestinal tract, especially in alcoholics and in patients with cirrhosis. Although commonly associated with acute drinking "sprees" it may also occur in the absence of alcohol intake. It characteristically may be recognized by the frequent occurrence of protracted nausea and nonbloody vomiting prior to the initial episode of hematemesis. The patient may exhibit repeated daily hematemesis of small quantities of blood. Fatal bleeding caused by this condition is rare. For this reason and because the entire gastric mucosa may be involved, surgery is usually contraindicated. Elimination of alcohol comprises the most important aspect of therapy. Since the patients may not tol-

erate anything by mouth, intubation is usually out of the question. The prompt use of parenteral antivagal and antiemetic drugs may prevent the superimposition of fatal hemorrhage from mucosal tears at the cardioesophageal junction caused by retching (Mallory-Weiss syndrome). Corrective therapy should be directed at the concomitant electrolyte imbalance, nutritional deficiency, and liver impairment.

CONCLUSIONS

In no clinical condition is the need for individualization and the hazard of generalization greater than in the management of patients with massive upper gastrointestinal hemorrhage. All hospitals differ, not only with respect to patient population, but also with respect to professional skills and laboratory facilities available. Accordingly, a protocol such as this may have more limitations than applications. Its primary purpose is to acquaint the newcomer with the local modus operandi. Its very preparation, however inadequate, emphasizes the need for cooperative effort and compels consideration of the problem from a hospital-wide point of view. To be useful, such a working plan must be constantly altered by new diagnostic techniques and advances in therapy.

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Progress in Internal Medicine

INFECTIOUS DISEASES

Twentieth Annual Review of Significant Publications

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IN THIS twentieth annual review it is fitting to pause for a brief review of reviews covering a great era in the field of infectious disease. Six Nobel prizes were awarded for the discovery and application of sulfonamide compounds, penicillin, streptomycin, and chlorophenothane, U. S. P. (dichlorodiphenyltrichlorethane; D. D. T.); for a means to cultivate the virus of poliomyelitis, and for a new biologic concept of viruses.

The death rate of pneumococcic pneumonia, subacute bacterial endocarditis, typhoid, plague, and typhus was reduced greatly by antibiotic therapy. Tuberculosis, syphilis, and other coccic infections also were so successfully treated that by 1949 the death rate from infectious diseases in the United States was the lowest ever recorded. In addition, the pressure of military necessity during the years 1941 to 1945 forced great advances in the knowledge of malaria, filariasis, rheumatic fever, enteric diseases, hepatitis, yellow fever, respiratory tract infections, and other viral diseases.

After many previous disappointments with chemotherapy, the advent of sulfanilamide was mentioned briefly in the review of 1937. By 1939, however, the rapid introduction of better sulfonamide compounds made the matter of first importance, but soon it was overshadowed by the antibiotic agents. Penicillin was mentioned cautiously in 1942. In the next year, despite its limited supply, many encouraging reports of its use removed any doubt of its value. It began to be used for syphilis and endocarditis. Thereafter, the spectacular results in the treatment of these and other infections led to overenthusiasm and, unfortunately, to indiscriminate use. Streptomycin was mentioned in the review of 1944. Its value in the treatment of tuberculosis and other infections not influenced by penicillin soon was revealed. Many other antibiotics were prepared, but only a few are of enough value to survive. Oxytetracycline, chlortetracycline, tetracycline, and others have broad bacteriostatic action in common. Chloramphenicol is important because of its effect on typhoid.

The discovery of an insecticide for mosquitoes aided in the control of malaria, the most devastating infectious disease in many parts of the world. The interference of malaria with military operations in World War II and the restricted supply of quinine led to the synthesis of superior therapeutic and prophylactic drugs. The secret of the preerythrocytic phase of plasmodia was revealed.

Cultivation in tissue culture of the virus of poliomyelitis provided a simple method for investigation. The viruses of poliomyelitis were classified into types, and many etiologic and epidemiologic problems were clarified. Vaccine, discussed in several symposiums after 1934, only recently has promised to be useful. The demonstration of the crystalline nature of a plant disease virus, for which a Nobel prize was awarded, stimulated research on the structure of other viruses, but this has not as yet led to significant practical advances.

In these two decades virology came of age, so to speak, and viruses were discovered to

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be the cause of diseases of the lungs, intestines, liver, heart, eyes, and, possibly, the genitourinary tract. The viruses of St. Louis, equine, and Japanese B encephalitis; lymphocytic choriomeningitis; mumps; Coxsackie disease, and several exotic diseases were established as neurotropic agents. Catscratch fever, rickettsialpox, epidemic keratoconjunctivitis, and infectious lymphocytosis were uncovered as "new" diseases. The discovery of the virus of influenza, first discussed in the review of 1935, provided both a standard and a stimulus for the study and classification of other common infections generally called colds. Vaccines for influenza viruses, though not wholly satisfactory, are now available. A form of nonbacterial pneumonia rose to pandemic proportions between 1939 and 1942. Because of its special characteristics, its resistance to therapy, and its low mortality, I described it as an entity probably caused by a virus. The severe epidemic diarrhea of the new-born received attention. A mild gastrointestinal disturbance occasionally appearing in epidemic form was shown to be an infectious viral disease and was called viral dysentery.

Viral hepatitis rose to prominence after 1942. The high incidence of infectious hepatitis in the Armed Forces was a serious medicomilitary problem. Serum hepatitis was an unfortunate sequel of the use of an anti-yellow-fever vaccine unwittingly prepared with hepatitis-virus-bearing serum. A safe anti-yellow-fever vaccine finally was devised. Yellow fever was discovered to be widespread among jungle fauna.

The invention of the electron microscope, the technique of cultivating viruses in eggs and in tissue culture, and the complement-fixation test provided useful tools for investigation in the viral era.

The reviews of 1935, 1936, and 1937 opened with the subject of pneumonia, then the third commonest cause of death in the United States. By that time, the custom of making etiologic diagnosis was accepted generally. Serotherapy was of chief interest, and, in 1939, 32 types of refined concentrated antipneumococcic rabbit serum were available for therapy. Sulfanilamide in that year was a therapeutic disappointment in the treatment of pneumonia, but a new era began with the introduction of sulfapyridine. In rapid succession, other improved sulfonamides were made, but all were obscured by penicillin. As a result of antibiotic therapy, the mortality rate of pneumococcic lobar pneumonia fell to less than 10%.

Before 1937, coccidioidomycosis was described as a fatal fungal disease. It was found, really, to be a common one in its mild form in certain arid regions. The mild forms had been unrecognized or misdiagnosed. Similar clarification came with the discovery of mild forms of histoplasmosis, a disease also previously regarded as invariably fatal. The cause was found to be a fungus of world-wide distribution. Diagnosis was aided by the use of the histoplasmin skin test and performance of biopsy. Many cases of both diseases had been mistaken for pulmonary tuberculosis. Order also was brought in the relationship and classification of leptospiral diseases, of the psittacosis-ornithosis group and among the world-wide rickettsioses. Q-fever and rickettsialpox were discovered. The Shigella, Salmonella, Group A beta-hemolytic streptococci, staphylococci, and the viruses of influenza, poliomyelitis, and Coxsackie disease were classified into specific types. For several years after 1934, the changed concepts of the pathogenesis of tetanus were reviewed. As an advance, one may include the deflation of the theory of focal infection pertaining to teeth and tonsils and the subsequent restraint of their unnecessary surgical removal.

Over the 20-year period there grew an increasing awareness of inapparent or mild forms of many infectious diseases, some of which outnumber the so-called typical case described in books. As examples, poliomyelitis, viral pneumonia, viral hepatitis, yellow fever, malaria, cholera, shigellosis, brucellosis, streptococcosis, typhoid, psittacosis, and typhus may be cited. Certain pathogens once thought to have limited tissue tropism

were shown to affect other parts as well, as for instance, in mumps, lymphocytic choriomeningitis, rubella, infectious mononucleosis, and meningococcic and rheumatic infections. Many infectious diseases were found to occur in birds, animals, and humans, and the knowledge often clarified epidemiologic and ecologic problems. In this category are Q-fever, lymphocytic choriomeningitis, leptospirosis, ornithosis, kala azar, tularemia, histoplasmosis, toxoplasmosis, yellow fever, and several encephalitic diseases.

It is hoped that at the end of the next decade or two some reviewer will have the enviable privilege of surveying advances of equal or of even greater significance in the control of infectious disease.

ANTIBIOTICS

Penicillin. — For uniformity, penicillin should be measured in milligrams, like all other antibiotics. If, according to the U. S. Pharmacopeia, one unit weighs 0.6γ, 100,000 units equal 60 mg., and so on. For the present, both measurements may be used.[1]

Penicillin given orally in amounts of 300,000 units (180 mg.) gives disappointing results. Absorption is irregular irrespective of the compound used or the age of the patient. Occasionally, there is no evidence of its absorption. Somewhat better results follow ingestion of 600,000 units (360 mg.).[2] Aqueous penicillin sodium is as effective as penicillin procaine in the treatment of staphylococcic infection in mice. Repository preparations release less penicillin initially, when in many instances it is most needed, than the more soluble compounds.[3] Severe reactions and one death after the injection of penicillin procaine have been reported.[4] Penicillin procaine may cause prolonged disease in hypersensitive patients.[5] Penicillin given orally may cause a severe anaphylactic reaction.[6] Eight fatal anaphylactic reactions to penicillin have been reported from New York City.[7] Relapse of infection by penicillin-sensitive bacteria is not always caused by the nature of the lesion or by failure of penetration of penicillin. Penicillin is rapidly bactericidal only for small numbers of "young bacteria." Its effect decreases with the increasing "age" of the bacterial population.[8] A crude filtrate of Penicillium culture has an antiviral action against poliomyelitis virus in monkeys.[9]

Local Therapy.—In surgical practice, according to Meleny and Johnson, antibiotics should not be used routinely for prophylaxis of clean wounds. Antibiotic prophylaxis, they write, is indicated for operations in contaminated fields in the eye, ear, oropharynx, gastrointestinal tract, or vagina. They recommend the local application of bacitracin, neomycin, or polymixin B after sensitivity tests reveal the appropriate one.[10] In Howe's experience, the rate of infection of so-called clean wounds has increased during the past five years. Since penicillin-resistant staphylococci were the cause in most cases, it is probable that the widespread careless use of penicillin is responsible for their presence. A program to control infection of wounds by preventing cross contamination is in force. Livingood reports on the effectiveness of erythromycin for the treatment of cutaneous infections caused by staphylococci and streptococci.[12] Poth believes that neomycin, if used widely as topical therapy, will cause the development of resistant bacteria and destroy its value as an intestinal antiseptic. The use of neomycin and other antibiotics should be restricted to serious conditions.[13]

Antibiotics and Staphylococcic Infection.—In Meleney's experience, the percentage of strains of penicillin-resistant staphylococci never rose over 43% and diminished to 22% last year.[10] This is different from most other reports, in which 60% to 80% are resistant. Of strains of staphylococci in patients who entered one hospital, 50% were resistant to penicillin and 10% were resistant to tetracycline. In patients treated with tetracyclines, 86% of strains became resistant in a four- to five-day period. The rate of increase in penicillin-resistance was greatest in patients treated with tetracyclines and was least among patients not treated with antibiotics.[14] In further studies, 65% were resistant to chlortetracycline, oxytetracycline, streptomy-

cin, and penicillin. In the year 1953-1954 over 90% of these strains were of phage Group III. The reason for the predominance of this type is unknown.[15]

The mortality rate for staphylococcic septicemia was 53% among 51 patients. The percentage of strains resistant to antibiotics was as follows: to penicillin, 70%; to streptomycin, 66%; to oxytetracycline, 47%; to chlortetracycline, 37%, and to chloramphenicol, 2.5%. The percentage of cultures sensitive to 1 unit/ml. was as follows: to erythromycin, 88%; to neomycin, 34%; to bacitracin, 26%; to oxytetracycline, 23%; to chlortetracycline, 21%; to penicillin, 17%; to streptomycin, 2.4%; to chloramphenicol, 0%. Patients treated with combinations of penicillin-bacitracin, erythromycin-bacitracin, or carbomycin-bacitracin survived.[16] A strain of Staphylococcus resistant to penicillin, streptomycin, chlortetracycline, chloramphenicol, and sulfadiazine was isolated from a patient who had received all of these agents.[17] The problem of bacterial resistance to antibiotics has been reviewed by Spink.[18]

The incidence of infections caused by erythromycin-resistant staphylococci also is increasing. This antibiotic should be used only when indicated and only for serious infections. It should not be given for chronic infections and never as a constituent of ointments or sprays.[19] According to editorial comment,

> Indeed in the present climate of opinion it may seem vain to preach the truth that trivial infections do not require antibiotics, that clean operations can be done without "antibiotic cover," and that the best dose of an antibiotic may be far more effective (as well as much safer) than the greatest amount which the patient will tolerate without obvious harm to his health.*

Despite the warning against the use of ointments or sprays just mentioned, two investigators state that the carrier rate of staphylococci was reduced for three months after the intranasal application of oxytetracycline cream for 10 days to patients in hospital wards. This was said to be accompanied by a fall in the number of patients who suffered cross infection contracted from nasal carriers of staphylococci.[22] Another author recommends the use of tyrothricin sprayed into the nose.[23]

Small-colony variants were derived from cultures of staphylococci grown in the presence of various antibiotics and from patients with staphylococcic infections during treatment with antibiotics. Bacteria from small colonies were avirulent, were more resistant to antibiotics than parent strains, and remained viable in the tissues of apparently normal animals. They reverted to the parent strain when cultured without antibiotics, and in some instances the reverted forms were more virulent than the original ones. The existence of small-colony variants may explain some failures in the treatment of staphylococcic infections.[24]

Side-Effects.—Oxytetracycline (Terramycin) caused side-effects in 8% of 603 patients. In treated patients the Staphylococcus as a secondary invader caused a scarlet-fever-like disease in eight and sore throat, urinary tract infection, or enteritis in others, and two cases were fatal.[25] In another study oxytetracycline in small daily doses was given to 100 persons, but side-reactions were so common that the trial was stopped. Gastrointestinal disturbance and other symptoms occurred in 69% and were severe in 18%. Side-effects therefore are more frequent than is believed. They may be masked by symptoms of the disease being treated.[26]

Hofer and McCaskey list three modes by which infections other than those for which treatment was given may develop during antibiotic therapy: (1) Insensitive bacteria may become predominant; (2) the antibiotic may stimulate their growth, and (3) antibiotics may cause a change in the tissue favoring infection.[27] According to Finland, the frequency of gastrointestinal disturbance and the presence of staphylococci as the predominant bacteria in the feces was greater in patients who received oxytetracycline than in those who were given chlortetracycline.[28]

* Reference 20. See also Reference 21.

Candida albicans (Monilia) was found in the sputum of 48% and in feces of 3% of 174 pneumonic patients. After treatment with oxytetracycline the percentages rose to about 60. No symptoms related to candidosis appeared.[29] According to Metzger and his co-workers, C. albicans rarely causes disease during or after antibiotic therapy. The mere increase in numbers of yeast cells in stools may reflect only a decrease of the resident bacteria. When yeasts cause disease, lowered resistance of the host seems to be the most important cause. The antiyeast activity of methylparaben and propylparaben (methylparahydroxybenzoate and propylparahydroxybenzoate) may control mycotic infection.[30] Among 3000 patients treated with one or more antibiotics studied by a group of observers, superimposition of a new infection occurred in over 2%. The organisms chiefly responsible were Proteus vulgaris, Pseudomonas aeruginosa, and C. albicans. In poliomyelitis patients treated with antibiotics to prevent pneumonia, superinfection was seven times higher than in untreated ones, and in patients with measles, 16 times higher. Superinfection occurred oftenest on the fourth or fifth day of treatment.[31] Treatment of mice with streptomycin increased their susceptibility to a streptomycin-resistant strain of Salmonella enteritidis, probably by disturbing the normal flora.[32] Treatment of gonorrhea with streptomycin gave rise to streptomycin-resistant gonococci. Penicillin-resistant gonococci have been reported by Zierz.[33] Others state that no penicillin-resistant gonococci have yet been found.[34]

Combined Antibiotic Therapy. — Polymixin B combined with oxytetracycline or tetracycline seems to act synergistically in inhibiting the growth of Ps. aeruginosa and in the treatment of urinary tract infection with this bacillus.[35] Use of a combination of chlortetracycline, oxytetracycline, and chloramphenicol in therapy has been suggested. Logic for the use of such a mixture seems to be as weak as that for combining three sulfonamide compounds instead of using a single one.[36]

Antibiotic Prophylaxis.—According to six collaborators, the administration of chlortetracycline to 20 patients with cardiac disease prior to oral surgery prevented bacteremia and the development of subacute bacterial endocarditis.[37] Chlortetracycline in amounts of 500 mg. daily was given for 19 months to diabetic patients, and similar patients received a placebo. At the end of that time, patients who had received antibiotics had fewer infections of the urinary and respiratory tracts and had "a better state of health" than the control patients. In the face of the figures they submit, one wonders why the authors are so timorous in their conclusion. They write "it appears that prolonged antibiotic prophylaxis may be of value in the management of diabetics."[38] It may be better to wait and treat infections as they arise. The rationale of using oxytetracyline and chlortetracycline for prophylaxis in abdominal surgical operations has been questioned.[39] A preparation containing sulfadiazine, sulfamethazine, and sulfamerazine (Sulfatriad), given prophylactically to patients after vaginal surgery, failed to prevent infection of the urinary tract. Infection with Streptococcus faecalis was even more frequent in those who received treatment than in control patients.[40]

Other Studies.—For studying the direct effect of antibiotics, Werner and his associates revived a method by which observations can be made on bacteria embedded in agar discs placed in the peritoneal cavity of animals.[41] When typhoid bacilli were studied, streptomycin, chlortetracycline, and chloramphenicol retarded their growth in vitro but only chloramphenicol was effective in the animal body. The difference of therapeutic action was attributed more to the drug-host relationship than to the drug-parasite one.[42]

Even though the causative bacteria were sensitive in cultural tests, bacteriostatic antibiotics were not effective in treating two patients with subacute bacterial endocarditis. They were used in patients who were hypersensitive to penicillin.[43] Chlortetracycline has no effect in lowering the mortality rate of

cholera.[44] Chlortetracycline, oxytetracycline, and chloramphenicol given orally have no influence on herpes simplex, plantar warts, lichen planus, pityriasis, dermatitis herpetiformis, or discoid eczema. Antibiotics are effective in the treatment of seborrheic dermatitis of recent origin when infection by susceptible bacteria is present.[45]

Toxicity.—Because of occasional serious and fatal hemopoietic suppression incident to its use, it is advisable to restrict the prescription of chloramphenicol to the treatment of typhoid, rickettsioses, and other serious diseases caused by organisms sensitive to chloramphenicol but resistant to other antibiotics.[46] Previously unreported prompt toxic reactions from streptomycin were observed in 34% of 91 patients. They were paresthesia, vertigo, lassitude, ocular discomfort, and difficulty in accommodation which occurred one to one and one-half hours after injection.[47]

Desensitization to penicillin and to streptomycin is said to be possible by the intramuscular, subcutaneous, intradermal, or (with penicillin) oral route by giving minute increasing doses over several weeks.[48]

New Antibiotics.—New antibiotics continue to be added to the long list of available ones, but, up to the present, no superior ones have appeared. Over 100,000 molds from soil samples were tested before erythromycin was found.[49] In the December, 1953, issue of *Antibiotics and Chemotherapy* these new antibiotics were described: aureolic acid, griseomycin, hygromycin, streptogramin, and amphomycin. Xanthocillin has been reported from Germany.[50]

Apart from a lower incidence of gastrointestinal disturbances, there do not seem to be any advantages of substituting tetracycline (Acromycin, Tetracyn) for oxytetracycline or chlortetracycline. It has the same range of bacteriostatic activity, and if bacterial resistance develops it is common to each.[51] According to other observations, tetracycline caused nausea, vomiting, and diarrhea in 5.5% of 217 persons. Four had allergic reactions.[52] Twenty-six patients with bacillary dysentery were treated with tetracycline with only one failure.[53]

Erythromycin was of little or no value in the treatment of seven patients with subacute bacterial endocarditis caused by streptococci or staphylococci. Bacterial resistance developed rapidly. The antibiotic should be used only if the causative bacteria are sensitive to it and if the patient is hypersensitive to penicillin.[54] Erythromycin has failed to influence the course of viral infections of the respiratory tract. During therapy, however, the incidence of carriers of hemolytic streptococci are reduced as compared with control subjects.[55] Erythromycin has no effect on influenza.[56]

DISEASES OF VIRAL AND OF PROBABLE VIRAL ORIGIN

Respiratory Tract Infections.—A short review of knowledge of acute infections of the respiratory tract [57] and another of colds [58] were published. According to a group of investigators,[59] the filtrable agent isolated by Hilleman and Werner [60] is the cause of one variety of minor acute respiratory tract disease. Samples of serum collected during an epidemic nine years ago had antibodies specific for the newly isolated virus. In another study, no difference of therapeutic effect was noted in patients treated with acetylsalicylic acid-acetophenetidin compounds as compared with those treated with penicillin.[61] Vaporized hexylresorcinol sprayed into office rooms has no effect in reducing the number of colds among the occupants.[62] (See Addendum on page 125.)

Influenza.—Large-scale field trials of influenza A vaccine have been made in England. Among more than 600 vaccinated persons, influenza occurred in about 3%; in an equal number of unvaccinated ones the attack rate was 4.9%. Other infections of the respiratory tract were not influenced. General reaction to vaccine occurred in less than 2% of those vaccinated.[63] Although the incidence of influenza was reduced by 40%, one wonders whether it is worth the trouble in average circumstances to vaccinate against so mild a disease. Vaccination of 20,000 persons in Holland with a vaccine composed of

three strains of virus failed to give significant protection against influenza caused by a strain not identical with those of the vaccine.[64] In the winter of 1952-1953, influenza A was first detected in December. It became epidemic four to six weeks later. A few cases of influenza B occurred.[65] Influenza virus B predominated in small epidemics in 1954. Virus A seldom was found.

Influenza virus C seems to cause disease intermediate in nature between the common cold and influenza of A or B type. Although C virus seldom is recovered from patients, serologic studies indicate that many adults have specific neutralizing bodies against it, suggesting that unrecognized infection is common. Attempts to infect volunteers with C virus were not successful except for a rise in antibody titer in four of six subjects. However, the investigators themselves apparently contracted influenza C during the experiment.†

Evidence of person-to-person transmission of influenza indicates how household groups are infected. An investigator confuses the issue when he states that influenza may come in epidemics in successive years or may disappear for 30 years. It is doubtful if so long an interval occurs. Many studies since 1933 reveal epidemics at yearly or in two- or three-year cycles. All evidence favors an affirmative answer to the question in the title of Simpson's paper.[68]

A study has been made by indirect means of the distribution of strains of influenza virus prevalent in the general population in different years. Antibody to A′ strains isolated since 1946 was found only in persons under 20 years of age, especially in children. Antibody to Type A PR strain isolated after 1933 was not detected in children under 12 but chiefly in those between 18 and 30, who probably had influenza of that type when it was prevalent. Antibody to swine influenza virus was not measurable except in persons older than 30. This further supports a view that the pandemic of 1918-1919 was caused by that type of virus. Influenza virus C, the most recently detected one, caused antibodies to appear in all age groups from 2 to 65 years.[69]

By electron microscopy, inclusion bodies composed of many particles about the size of those of the virus tested can be demonstrated in the cytoplasm of cells in the lungs of mice which have inhaled the virus 15 hours previously.[70] In studies with dark-field microscopy, the infective particle of influenza virus is visualized as a fragment of the cell cytoplasm in which it grows. It consists of a closely aggregated mass of virus protein enclosed in a cell membrane.[71]

When eggs are infected with both influenza A and influenza B virus, a new type of virus evolves with antigenic properties of both parent strains. The doubly antigenic virus arises from what is called phenotypic mixing. The ability of virus particles to give rise to different strains is due to heterozygosis or diploidy. On further culture, the new virus does not reproduce itself, but yields parent types.[72] New complex chemical compounds inhibit the growth of influenza and mumps virus in culture in eggs and in mice without harming the hosts.[73]

Viral Pneumonia.—During an epidemic of mild respiratory tract disease in 1952-1953, 20% of persons affected had viral pneumonia. An agent, presumably a virus, was recovered from throat washings of patients with pneumonia and from some of them without pneumonia. It was not transferable to mice or guinea pigs. Specific neutralizing and complement-fixing antibodies for the agent appeared in the patients' blood.[60] The virus may be the same as, or related to, a cytopathogen recovered by others from adenoids.[74] If the agent is the cause, the observations add more evidence, if more is needed, that viral pneumonia is caused by a virus and often is the severest form of a mild infection of the respiratory tract.

In a study of viral pneumonia in Glasgow, Grist found that only a small minority of pneumonias he observed were viral infections detectable by laboratory tests. Over three years, evidence of ornithosis was found

† References 66 and 67.

in only 0.4% of cases, and cold agglutination, in the same number. Antibodies against Q-fever were not found. The majority of pneumonias, he writes, were caused by bacteria susceptible to antibiotic therapy.[75] No mention is made of viral pneumonias for which there are no diagnostic laboratory tests. In my experience in Lebanon in the winter of 1954, viral pneumonias outnumbered pneumococcic lobar pneumonias 10-fold. As mentioned in the preceding paragraph, viral pneumonias are the severe forms of a widespread epidemic of mild infection of the respiratory tract. A number of victims, including myself, were ambulatory, and pneumonia, occasionally bilateral, would not have been diagnosed without roentgenography.

Because it usually is a mild disease and of low mortality, it is difficult to gauge the effect of antibiotic therapy of viral pneumonia. When statistical computation is needed to prove the advantage of any form of therapy, it is reasonable to assume its value not to be great. According to one group of investigators, chlortetracycline, oxytetracycline, and chloramphenicol shorten the duration of illness, especially in the rare severe cases.[76] If this be the case, it either provides the first example of beneficial effects of antibiotics in a disease of viral origin or suggests that the pneumonia in question was not caused by a virus. The possible antipyretic effect of chlortetracycline must be considered in evaluating results of therapy.[77]

Epidemics of bronchitis and pneumonia occurred among young children in London in the winters of 1949 and 1950. They were not caused by the virus of influenza, psittacosis, or Q-fever, nor were bacteria involved. The cold-agglutination test gave positive results. The epidemics may have been caused by the agents which cause colds in adults.[78]

Serologic tests on samples of blood submitted for diagnostic aid seldom reveal evidence of psittacosis or ornithosis. However, tests on samples collected from groups of people in farming and poultry-raising districts gave a positive complement-fixation reaction in titers of 1:32 or more in from 9% to 25%. Thirty-seven cases of ornithosis were observed in patients with mild disease of the respiratory tract. Since the disease usually is mild, diagnosis often is missed.[79]

In a study of 300 cases of heart failure, the precipitating cause in 156 cases was infection of the respiratory tract. It is particularly dangerous in patients with cor pulmonale and was the cause of failure in 74 of 76 patients.[80]

Viral Hepatitis.—Although viral hepatitis now is statistically recorded as the fifth commonest infectious disease, there is no reason to suppose that its incidence is increasing. The increase in reported cases is almost certainly the result of greater awareness and better diagnoses, especially of mild cases. The fatality rate is low. Five-sixths of deaths therefrom occurred in patients over 15 years old.[81] In a general review of the subject, Neefe points out how few significant advances in knowledge have been made in recent years.[82]

The transfusion of whole blood and plasma, in spite of precautionary measures, still is responsible for the development of hepatitis in from 0.45% to 20% of recipients. Because of the potential seriousness of serum hepatitis caused by B virus, the possible value of transfusions should outweigh the risk of infection. Report is made of studies on the problem in three papers in the March 27 issue of *The Journal of the American Medical Association,* in which 23 authors collaborated. The first proved carrier of the virus of viral (infectious, IH or A virus) hepatitis was described. The agent was present in the stools of carriers for indeterminate periods. The virus may be present in the blood for more than five years. The suspected existence of carriers of B virus in whom there was no clinical evidence of a previous acute attack of hepatitis was proved. Possibly, also, the persistence of the virus in patients at times may be a cause of chronic hepatic disease and eventual cirrhosis.

In an epidemic period, 5 of 34 apparently healthy persons showed changes in their blood suggestive of inapparent infection. Such cases may be relatively common, espe-

cially in persons under 40, who may serve as uncontrollable spreaders of infection.[83] Hepatitis may be transmitted by dental procedures.[84]

Three fatal cases of what appeared to have been serum hepatitis have been observed in infants under 4 months of age. Diaplacental transmission of the virus during hepatitis in mothers is rare but is possible. Several instances have been observed of either infectious or of serum hepatitis.[85] Congenital disorders as a result of material disease may occur if hepatitis occurs in early pregnancy, but they are less frequent than those following rubella.[86]

Controversy about the residuals of viral hepatitis continues. While, as just mentioned, prolonged, asymptomatic viremia may end in chronic hepatic disease, other studies on patients who had had overt icteric viral hepatitis four to six years previously failed to reveal any difference from control subjects as measured by tests of hepatocellular function or by hepatic biopsy.[87] Fourteen other patients with evidence of hepatic disease six months after an attack of viral hepatitis were studied for six years. Of these, nine died and five recovered completely. The condition obviously does not always pursue a relentless fatal course. The severity of the original illness or the age of the patient were of no prognostic import. Continuously abnormal results of laboratory tests of hepatic function and long duration of symptoms are bad omens.[88]

Conflicting views persist in regard to methods used to sterilize plasma. According to one investigative team, if pooled plasma collected from persons who have not had viral hepatitis is stored in a liquid state for six weeks at room temperature there is no risk of its transmitting the virus of hepatitis. Virus deliberately added to plasma dies out when subjected to such storage. No significant chemical changes occur.[89] However, in tests by others, icterogenic plasma stored for three months caused hepatitis in 3 of 5 volunteers and plasma stored for six months caused the disease in 1 of 19 volunteers.[90] Similar observations were made in a British survey.[91] Evidently no way has yet been discovered to render plasma safe. Fresh whole blood and small-pool plasma (8 to 10 donors) are least dangerous. The virus of serum hepatitis is unusually resistant to ultraviolet radiation, to chlorination, and to heat. The virus in plasma is viable after heat of 60 C for four hours.[92]

Corticotropin may shorten the course of viral hepatitis, but the difference as compared with nontreated patients is not significant. Treatment does not make the disease worse.[93] Studies by Nelson and his co-workers confirm the views of Chalmers and others published previously that activity far in excess of that usually prescribed for patients with acute hepatitis has little or no effect on the rate of recovery or on relapses.[94]

Gamma globulin, 0.02 ml. per kg., protected persons in an institution against icteric hepatitis. After eight weeks many anicteric infections continued to appear. Half the dose also was effective but may have permitted anicteric and inapparent infection to occur. Passive immunity lasts about two months or less, unless the treated person is continually exposed to infection.[95]

After many fruitless attempts by others, Wildführ reports success in isolating the virus of hepatitis. A virus was revealed when hamsters, birds, and eggs were inoculated with serum or bile from patients. Viruses of serum hepatitis and infectious hepatitis both were recovered. By electron microscopy, the virus appeared to be composed of particles 35μ to 50μ in size.[96] The observations await confirmation.

A virus which causes jaundice without striking changes in the liver of racoons has been studied. It probably is not related to the viruses of feline or canine distemper or to canine hepatitis.[97]

Poliomyelitis.—In a report of the National Advisory Committee for the Evaluation of Gamma Globulin, the conclusions are as follows: The use of gamma globulin prophylactically does not yield statistically measurable results when used on a large scale. Its value in preventing poliomyelitis has not been demonstrated. When used among familial

associates of patients with poliomyelitis, it does not alter the classic pattern of familial aggregation of cases; it has no influence on the severity of paralysis or on the proportion of nonparalytic cases.[98] In Hammon's restudy of the matter, gamma globulin had value if given after exposure had occurred. A new analysis of old data covering laboratory-confirmed cases shows that clinically diagnosed cases in those who received globulin were due either to Type 1 poliomyelitis or to agents other than poliomyelitis.[99] In another study, gamma globulin injected during subclinical poliomyelitis had no effect on the course. Inapparent infection may develop in the weeks after injection.[100] Despite these disappointing reports, the Public Health Service announced that twice as much gamma globulin as used before is now available for use in groups larger than a single family unit.[101]

Analysis of results of the mass trial of poliomyelitis vaccine in the spring and summer of 1954 is awaited with interest, and in some quarters with skepticism. According to newspaper report, vaccination is a success. Bodian critically reviews the problem of immunization. The development of a vaccine which prevents paralysis is desired even if it is of low potency. However, if the lifetime risk of acquiring poliomyelitis in the United States is about 1:1000, great precautions must be taken to be sure that the prevention is not worse than the disease.[102] In a general review of vaccination for viral diseases, Cox cites rabies, smallpox, and yellow fever vaccines as the most successful. In almost all instances vaccines to be effective must be live "attenuated" viruses which retain a specific antigenic structure. No tested practicable vaccine against poliomyelitis is available as yet. The one in current use is nonviable and is of doubtful value. An "attenuated" living virus given orally would seem preferable.[103] Perhaps the nonneurotropic variant isolated by Li and Schaeffer may be successfully used. As an immunizing agent it has induced a good antibody titer and a high degree of resistance against a virulent strain.[104] Other investigators also isolated variant strains of each of the three types of poliomyelitis virus. They are not avirulent but cause a few neuronal lesions without paralysis in monkeys when inoculated by routes other than intraspinally. The modified viruses are immunogenic.[105] In tissue cultures noncytopathogenic forms at times induce resistance against pathogenic ones.[106] Kaprowski adapted Types 1 and 2 poliomyelitis virus to mice and cotton rats, which resulted in "attenuation" of the viruses. Feeding these strains to humans did not cause disease, but the virus was excreted in their stools. Homologus neutralizing antibodies developed in each. The recovered virus still was of low pathogenity when inoculated intracerebrally in monkeys.[107]

There no longer is any doubt about the relationship of poliomyelitis and the tonsils. According to Anderson and Rondeau, the absence of tonsils increases the risk of bulbar poliomyelitis fourfold, probably by permitting direct invasion in the throat. It occurs at all ages, regardless of the time elapsed after operation.[108] Among 85 patients with bulbar poliomyelitis reported elsewhere, 86% had had tonsillectomy. Bulbar involvement developed in only 14% of those whose tonsils were present.[109]

Enders has reviewed recent advances in the technique of cultivating the virus.[110] New clinical, diagnostic, therapeutic, and prophylactic precedures are discussed in a series of papers in the Sept. 4, 1954, issue of *The Journal of the American Medical Association.*

In a study of 73 persons under 15 years of age who were in close contact with poliomyelitis, 29 had no Type 1 antibodies and were considered to be nonimmune. Of these, 26 (90%) were infected by contact. Of 19 older contacts, 10 were nonimmune but only 2 of these (20%) became infected. Young children and infants had milder disease and less paralysis. The ratio of inapparent infections to overt disease was 1:1, in contrast with a previously estimated ratio of 100:1.[111]

In a study of multiple cases in households, the probability that more than one case will

develop is greater when the initial case is paralytic than when it is nonparalytic, and the age span of susceptibility is increased. The prognosis in subsequently developing cases is worse if the initial case is paralytic.[112] An explanation of these observations is difficult. Even though the severity of symptoms varies according to the resistance of the host, the virus presumably is constant in "virulence." The conclusions have been questioned elsewhere, and the possibility was mentioned that some of the nonparalytic cases may not have been of poliomyelitis.[113]

Types 2 and 3 poliomyelitis viruses when lyophilized do not lose virulence. This fact raises the epidemiologic question of their possible transmission in the dry state by air.[114]

Poliomyelitis virus was discovered in the placenta and fetus after infection had occurred during pregnancy.[115] Other cases in a mother and a 13-day-old infant were reported.[116] Minto made the curious observation that among 1183 patients with poliomyelitis only one had blond hair and blue eyes; the rest were brunettes.[117]

In histologic studies of the brain, less than 15% to 20% of the large motor cells are found to be injured. This is said to account for the absence of symptoms arising in the motor cortex. In the cerebellum, never are more than 8% of the cells involved. Although the injury is mild, it is diffuse, suggesting the spread of infection by way of the blood.‡

Poliomyelitis-like Disease.—Outbreaks of a poliomyelitis-like disease have been observed in England, Iceland, Australia, and New York State. The high morbidity rate, the winter incidence, its mildness, its long duration, and the low mortality-rate are not characteristic of poliomyelitis. Clinically there are fever; pains in the head, neck, and back; tenderness and flaccidity of groups of muscles, and sensory changes. Paresis and slight pleocytosis of the spinal fluid occur. There is no evidence of activity of the viruses of poliomyelitis, Coxsackie disease, or mumps; of leptospirosis, or of other known causes of encephalitis.§

Coxsackie Disease.—During an epidemic of poliomyelitis, a number of persons in a community had an unclassifiable minor illness. There were sore throat, fever, and oral vesicles suggestive of herpangina. Stool specimens contained Type 2A Coxsackie virus. Adult family members developed specific neutralizing antibodies but did not excrete the virus.[123] Elsewhere, in a school for mentally defective children, 11 inmates had a febrile illness with meningeal disturbances called aseptic meningitis. Coxsackie virus Type 2B was present in the stool of four patients and in the throat and spinal fluid of one each.[124] The virus may have caused the disease, but it also may have been a commensal, as it occasionally is during poliomyelitis.

When two unrelated viruses are inoculated together they may grow independently; one may interfere with the other and suppress its effects, or one may enhance the invasiveness of the other. In experiments with Coxsackie and poliomyelitis viruses, animals inoculated with both survived twice as long as those inoculated with poliomyelitis virus alone.[125]

Encephalitis.—By applying cross neutralization tests, Smithburn classified arthropod-borne viruses into two groups and confirmed the scheme of Casals and Brown. Relationship was found between viruses from widely separate parts of the world. Group A consists of Eastern, Western, and Venezuelian equine and Sindbis and Semliki Forest viruses. In Group B are dengue, Ilhéus, Japanese B, Ntaya, St. Louis, West Nile, yellow fever, Russian, Far Eastern, and louping-ill viruses. The relationships suggest evolution from common ancestors.[126]

A virus has been isolated from patients in Israel with acute meningeal disease. It is neutralized by antiserum against West Nile, Japanese B, and St. Louis viruses.[127] West Nile virus has been detected in pigeons and crows in Egypt,[128] as other encephalitic

‡ References 118 and 119.

§ References 120-122.

viruses have been found previously in American birds. Patients with neoplastic disease were inoculated with West Nile virus. In 89% there was no clinical evidence of infection and the rest had mild encephalitis. The observations show how difficult it may be to diagnose viral disease: During early viremia there are no symptoms, and when symptoms appear virus can no longer be recovered from the blood or spinal fluid. Attempts fail to reveal virus in the urine, stool, or throat, and antibodies in the blood are not demonstrable for three weeks.[129]

Despite the use of a vaccine which met the standards of safety, among 327 persons vaccinated against Venezuelian equine encephalitis, 14 were infected and had viremia. Subsequent injection of the vaccine into animals failed to reveal live virus. Perhaps humans are unusually susceptible.[130]

A form of encephalitis probably transmitted by ticks has been encountered in Austria. Sixty-four persons were sick, and all recovered. The virus is said to be related to louping-ill and to the tick encephalitis virus of Czechoslovakia and Russia.[131] Another form of encephalitis in humans is thought to be caused by the virus of sporadic bovine encephalitis. Complement-fixing antibodies were demonstrable in the blood of 15% of 488 samples of human serum.[132] French observers report meningitis caused by a virus of bovine origin related to foot-and-mouth disease.[133] Encephalitis also occurs during cat-scratch disease.[134] Severe lesions in the brain and spinal cord may be caused by rubella virus.[135]

Rabies.—Three cases of rabies were undiagnosed during life. There were bizarre uncharacteristic symptoms of disturbances of the central nervous system. Contact with suspected or actually rabid dogs had occurred.[136] Persons in Florida and Pennsylvania were bitten by rabid bats. In two cases the attacks were unprovoked.‖ In one instance, in spite of advice to the contrary, the wound was cauterized, which is an illogical, harmful procedure.[139] The bats were insectivorous and of different species. Apparently even nonsanguivorous ones are natural hosts of rabies virus.[140]

Neuroparalytic accidents in the form of transverse myelitis, polyneuritis, and pleocytosis of the spinal fluid occurred in 17 persons out of 1400 vaccinated with Semple vaccine. Lesions were of two kinds, perivascular myelinoclasic and neuronitis of the Guillain-Barré type.[141]

Other Viral Diseases. — Enders and Peebles for the first time have isolated the virus of measles in tissue culture. Eight viruses were grown from blood or washings of the throat from five patients. Antibodies which develop during the disease, when applied to cultures, suppress the characteristic cytopathogenic effects of the viruses.[142] A special technique gives immunologic evidence that the viruses of varicella and herpes zoster also are propagated in tissue cultures.[143] Anderson apparently has cultivated rubella virus.[144]

The cerebrospinal fluid from patients with mumps meningitis when injected intradermally in other patients with mumps is said to cause a hypersensitive reaction. The procedure may serve as a diagnostic test. Reactivity may be demonstrated as long as two years after mumps.[145] Electrocardiographic evidence of myocarditis is present in about 6% of adults with mumps, and abnormality of the spinal fluid, in 54%. Orchitis occurs in 68% of males.[146]

In the Glasgow 1949 epidemic of smallpox, unvaccinated persons in close contact with patients were not infected. It was suggested that the disease is not as contagious as chickenpox or influenza, probably because the virus is deep in the skin and is not released until the vesicles rupture. Virus was not detected in the saliva during the first two days of preeruptive fever.[147]

Histopathologic evidence of yellow fever in monkeys found dead in the jungle in Costa Rica serves as a warning of an impending epidemic, similar to the death of rats before an epidemic of plague.[148] Anti-yellow fever vaccine caused two cases of encephalitis in

‖ References 137 and 138.

infants. The virus of the vaccine may be neurotropic in infants.[149]

Diseases of Probable Viral Origin.—It is uncertain whether infectious mononucleosis is a syndrome or an entity. One group of observers believes that there are sporadic and epidemic kinds, probably caused by different agents. The former generally is more severe, with low infectivity, high fever, and lymphocytosis exceeding 50%, and the heterophile test is positive after absorption. The epidemic form is contagious and mild; erythema is common; the lymphocytes seldom exceed 50%, and the heterophile test often gives a negative result.[150] Infectious mononucleosis may be mistaken for diphtheria if a pharyngeal exudate is present,[151] for herpetic stomatitis, and for viral hepatitis. French observers distinguish hepatitis from mononucleosis by observing the histologic changes in portions of liver obtained by biopsy in the first two weeks of the disease.[152]

Among 100 cases of cat-scratch disease, only 12 had no known contact with cats. An initial lesion was present in 80, and the regional lymph nodes were affected in 72, with suppuration in 47. An intradermal reaction against injected antigen is said to be of diagnostic value. This reaction, together with contact with cats, is helpful in differentiating the disease from tularemia, lymphoma, lymphogranuloma, infectious mononucleosis, and tuberculosis. Encephalitis, erythema multiforme, and abdominal pain may occur.[153] A fatal case was observed in an infant.[154]

Controversy persists about nongonococcic urethritis. Some regard it as a bacterial infection not venereal in origin in sexually active persons.[155] Wilcox believes that bacteria play no role and that inclusion bodies seen in urethral smears may be unrelated to the disease. He regards it of venereal origin.[156] The infection or one like it has been seen often in the Armed Forces. Of 3400 patients with urethritis in an 18-month period, nearly half had nonspecific infection. Of these 82% had had recent sexual contact. The course lasted from 1 to more than 30 days, usually 2 to 5 days.[157] In other observations on military men and their wives, genital warts and condyloma acuminata resulted from implantation of the causative virus during coitus.[158]

Reviews of the subject of epidemic hemorrhagic fever continue to appear without new facts to record.[159] The disease developed in a veteran in Kansas 3 weeks after he had left Korea. It must be kept in mind if serious acute disease occurs in persons who have been in an endemic area.[160] Epidemic keratoconjunctivitis, which was prevalent in the early 1940's has recently reappeared.[161]

An epidemic of a mild febrile exanthematous disease of children different from the known ones occurred in Boston in 1951. Coxsackie virus was isolated from two victims, but apparently it was not related to the disease. Seven other cytopathic filtrable agents were recovered. Serum from 9 of 11 patients significantly neutralized at least one of the strains. The authors point out that specific diagnoses by isolation of the virus or by serologic tests is possible only with variola, vaccinia, and herpes simplex. Measles, rubella, and roseola infanticum can be diagnosed only on clinical and epidemiologic grounds.[162]

A critical review has been made of tests used in the diagnosis of viral and rickettsial disease. The principles involved, the difficulties in technique, interpretation of results, and the application of the neutralization, hetrophile-antibody, cold-agglutination, complement-fixation, and other tests are outlined.[163]

Miscellaneous Viral Studies.—Intranuclear inclusions and cytoplasmic masses have been found in a kind of wart or papilloma. Electromicroscopy shows round bodies arranged in closely packed spheres.[164] Studies have been made to find out why viruses have special tissue tropism and vary widely in their ability to grow in different tissues. Apparently nutritional needs such as amino acids, B vitamins, and biologic reducing agents are deciding factors.[165]

In 1909, Dr. F. G. Novy stored glycerinated rat blood containing an unclassified filtrable neurotropic virus in company with spirochetes. Thirty-five years later, after

storage in the refrigerator and at room temperature, both virus and spirochetes still were living.[166] Some viruses seem to be durable under these conditions. Doubt therefore may be cast on the efficacy of storing plasma at room temperature to kill other viruses especially that of viral hepatitis, mentioned previously in this review.

Experiments by Fong and Louie showed that yields of viral hemagglutinin are greatly increased by inoculating cortisone-treated embryonated eggs with interfering doses of an inactivated virus followed by a challenging dose of virus. The yield of virus is 1000% or more higher in cortisone-treated eggs than in untreated ones.[167] The time factor is important in viral interference reactions. St. Louis virus after intranasal inoculation offers no protection against infection with Western equine virus inoculated by the same route 2 to 24 hours later. However, protection occurs if the challenge inoculation is made 72 to 96 hours or even 10 days later.[168]

According to Gross, leukemia may be caused by a viral agent. Theoretically the virus is dormant and is provoked into activity by some stimulus. An infectious agent is suspected because multiple cases occur in some families.[169] One wonders whether a genetic factor is not a more likely explanation.

DISEASES CAUSED BY BACILLI

Tuberculosis.—The death rate from tuberculosis as computed by a life insurance company is at a new minimum—10.2 per 100,000. However, there still are about 400,000 active cases in the United States. More than half of all deaths from tuberculosis now occur after the age of 55. Older persons are the chief victims of the disease and are a major source of its spread.[170] Among homeless men in Minneapolis, the rate of tuberculosis was 55 times higher than in the general population. The danger of dissemination is great, since vagrants often seek temporary employment as food handlers and dishwashers.[171] The source of infection of five cases of tuberculous adenitis in children was traced to milk from a cow with tuberculous mastitis. The importance of recognizing adenitis caused by bovine tubercle bacilli is emphasized.[172] Hemoptysis in inactive tuberculosis does not always signify a relapse. In 21 of Charr's patients, hemoptysis indicated relapse in only 3; in the rest it was due to other causes.[173]

At a meeting of medical directors of life insurance companies, Medlar described the initial lesion of pulmonary tuberculosis as a lobular one 2 mm. in diameter. It may resolve, fibrose, calcify, or become necrotic and liquefy. If, by chance, it forms in the lower and anterior portions of lobes, it usually heals; if it is in the upper and dorsal areas, disease is more likely to develop. According to Long, renal tuberculosis in the past was fatal in 60% to 85% of cases. Now, with appropriate therapy, over a five-year period it is 8%.[174]

Unsolved problems of tuberculosis have been discussed by Dubos.[175]

Treatment.—A preliminary report of observations on 1600 patients indicates that therapy with isoniazid and *p*-aminosalicylic acid is as effective as with isoniazid and streptomycin. The combination of the three drugs is no better than of two. Increased dosage of isoniazid increases the number of toxic reactions but not its therapeutic value.[176] Doonief and Hite report on continuous treatment with streptomycin, *p*-aminosalicylic acid, and isoniazid in varying combinations in 52 patients for 13 to more than 52 months. Clinical and roentgenologic results were said to be excellent, and there were no relapses. Toxicity from the drugs was slight, and tolerance made long-term therapy possible.[177] Patients with Addison's disease and tuberculosis may be treated safely with cortisone if they receive at the same time the three antibiotic agents just mentioned.[178] Goodwin has published a brief review of the newer ideas in the management of pulmonary tuberculosis.[179]

Iproniazid (Marsilid) effectively controls tuberculosis of joints and soft tissues in children, sometimes without surgical intervention. Because of effects of the drug on the nervous system, doses over 4 mg. per kg. of

body weight are dangerous.[180] For unexplained reasons, iproniazid is effective also in the treatment of serious nontuberculous bone and joint infections which resist antibiotic therapy.[181]

Tubercle bacilli may survive in healed pulmonary lesions after prolonged therapy. Direct inoculation of guinea pigs fails to reveal bacilli in many cases, but they have been cultivated after incubation in media for 9 to 12 weeks.[182]

Primary infections with drug-resistant tubercle bacilli have been reported since 1951. Nine more examples have been encountered. In several patients, bacilli were resistant to *p*-aminosalicylic acid, and in one, to streptomycin also. Three patients had had tuberculosis before the drugs were in general use and presumably were superinfected with resistant bacilli derived from other streptomycin-treated patients.[183] Tubercle bacilli which become resistant to isoniazid during treatment may again become sensitive, in some cases after the addition to streptomycin and *p*-aminosalicylic acid to the culture media.[184]

Tuberculous Meningitis.—Isoniazid alone or combined with streptomycin and *p*-aminosalicylic acid seems to prevent the development of meningitis in patients with miliary tuberculosis as compared with those not treated with isoniazid.[185] In two studies, comparison has been made between results of therapy with (*a*) streptomycin given intramuscularly and intrathecally, *p*-aminosalicylic acid, and/or thiazolsulfone and (*b*) streptomycin given intramuscularly and isoniazid. The latter combination apparently is the best.¶ Although recommended by some, the addition of *p*-aminosalicylic acid hardly seems necessary.[188] Ten patients were treated with isonicotinic acid hydrazide alone and recovered. Survivors were well 20 to 23 months afterward. Toxic side-effects occurred in several.[189]

In spite of possible harm of using cortisone in tuberculosis, its use in a few cases of meningitis seems to be helpful. Infection must, of course, be treated at the same time with streptomycin and adjuvant drugs. Five of seven patients recovered. There was no evidence of spread of infection. Microscopic study in the two fatal cases revealed a striking lack of cellular reaction. Suppression of cellular response may serve to prevent the development of adhesions and fibrosis.[190] Unfortunately, adhesions and blockings are not prevented by the intrathecal injection of streptokinase. Temporary success was attained in only one of nine patients. It is a dangerous procedure.[191]

Other Studies.—The inability to demonstrate circulating antibodies in tuberculous patients may be due to "masking." By fractioning the protein of the blood, hemagglutination and complement-fixing reactions can be demonstrated.[192] Bacteriophages active against tubercle bacilli have been discovered.[193] As in the case of other bacteria, they may be of value in separating tubercle bacilli into specific types.

Prevention.—According to editorial comment, the bulk of evidence favors the use of BCG vaccine for the prevention of tuberculosis in communities where other measures are not feasible. Vaccination also is recommended for tuberculin-negative persons who are unusually exposed to infection.[194] Myers, however, again cautious against its use, despite the favorable reports from European sources, for the following reasons: Cultures used for vaccine vary greatly in biologic characteristics; vaccine occasionally causes tuberculosis when inoculated into animals, and vaccinated persons have developed fatal tuberculosis.[195] Two fatal cases have been described. BCG vaccine given to a 24-year-old man apparently caused generalized tuberculosis five years later.[196] In a boy aged 7, generalized tuberculosis of the lymphatic system developed two weeks after vaccination and failed to respond to therapy. Fortunately, fatal cases are rare.[197] Lupus vulgaris apparently was caused in 11 vaccinated persons.# According to a Dutch physician, vac-

¶ References 186 and 187.

References 198 and 199.

cination against pertussis would save more lives than vaccination with BCG.[200]

Leprosy.—Arnold rightly criticizes the tendency to call leprosy hansenosis. Eponyms are undesirable; yet the term brucellosis is accepted. The stigma of leprosy can be removed better by education, as in the case of syphilis, tuberculosis, or cancer. He asks if the names schaudinosis, kochosis, or virchowosis, respectively, would serve any useful purpose.[201]

In an African survey, 21% of lepers were children. The increase in incidence was greatest between the ages of 5 and 14 years, suggesting that exposure to infection occurs in early life by close daily contact. Prevention of infection in children is the key to eliminating leprosy from a community.[202]

Observation on 1000 lepers, in harmony with previous reports, showed that treatment with sulfone compounds, especially diaminodiphenylsulfone, is a major advance in therapy. In 117 patients reexamined eight years after beginning treatment, the disease was clinically inactive, and, in most, the lesions contained no bacilli.[203]

Brucellosis.—In Spink's study of family groups, many persons had been exposed to infection with Brucella; the tissues of some were invaded, but relatively few were sick.[204] One may add that still fewer develop chronic disease. Brucellosis is not a common disease. It is surprising, therefore, that one investigator was able to collect over 420 cases, including 378 cases of the chronic form in a five-year period. Further surprise is occasioned by report that splenectomy and Brucella antigen were used in therapy. In spite of the well-known inefficiency of antibiotic therapy for chronic infections, chlortetracycline reportedly was said to be curative in 182 of 207 patients.[205]

Even though the infection persists and Brucella organisms remain in the tissues and blood, therapy with cortisone and corticotropin caused more rapid improvement in severely sick patients than any other medication.[204] Nevertheless, as Magill and his associates conclude, cortisone must be used with caution. Relapse occurred in 30% of patients treated with a combination of cortisone, oxytetracycline, and dihydrostreptomycin.[206] The hormone should not be given for more than five days. It apparently controls the theoretic hypersensitive state against the action of a somatic antigen or endotoxin.

Three cases of human brucellosis followed accidental inoculation with B. abortus 19, a strain used for the immunization of cattle and supposedly harmless to man.[207] Studies in Germany reemphasize the frequency of brucellosis in veterinarians. Of 2400 serums tested, 41 gave evidence of previous infection and of these 21 came from veterinarians.[208] If guinea pigs inoculated with one strain of Brucella are reinoculated with another, the Brucella organisms of the first inoculation remain in tissues for months but the bacilli of reinoculation disappear rapidly.[209] A somatic antigen or endotoxin has been demonstrated in mice. Its toxicity is the same whether it is made by Brucella of high or low invasiveness. Perhaps the endotoxin accounts for the toxemia in patients infected with strains of Brucella of low invasiveness, as, for example, B. abortus 19, mentioned above.[210]

To avoid unreliable results from agglutination tests with faulty antigen, a standardized Brucella diagnostic antigen soon will be available commercially. Titers less than 1:100 are apt to be unspecific.[211] Occasionally, strains of Brucella cannot be classified accurately. Probably these are variant ones derived from known strains.[212]

Tetanus.—There is disagreement about the therapeutic value of curare. According to Shackleton, who reviewed the history of the treatment of tetanus, muscle relaxants to relieve spasm are disappointing. No preparations of curare are safe enough to use.[213] In editorial comment on his paper it is surprising to find no mention of Abel's theory of blood-borne transmission of toxin. Instead, toxin is said to reach the bulbar nuclei by the unlikely way of the regional nerve trunks.[214]

Lassen and his co-workers, on the other hand, treated four patients with curare, long-continued general anesthesia, and continuous manually controlled positive-pressure ventilation through a tracheotomy tube. In addition, tetanus antitoxin 20,000 units and penicillin procaine 300,000 units (180 mg.) were given. One patient was treated in this manner for 17 days. Three patients recovered, and one died from septicemia.[215]

Salmonella Infections.—Neither chloramphenicol nor cortisone cure typhoid; they only aid the patient to combat the infection. Cortisone is unnecessary in mild and moderately severe cases, but together with chloramphenicol it occasionally appears to be life-saving and shortens the course of severe toxic cases.[216] New preparations of chloramphenicol for intravenous and intramuscular injection are available for use when oral therapy cannot be applied.[217] The therapy of typhoid has been outlined by Woodward and his associates.[218]

Vaccination does not always prevent typhoid. Of 112 typhoid patients in a military camp, 50 had been vaccinated during the previous year. All recovered after treatment with chloramphenicol.[219]

Chimpanzees fed bananas containing S. typhosa developed typhoid in four to six days which resembled the disease in humans.[220] An unusual biliary carrier of S. typhimurium was treated by cholecystectomy. No more bacilli were said to have been found in the stools afterwards.[221]

Cockroaches which inhabit sewers can invade buildings through sewer pipes even if traps are present in the plumbing system. Various kinds of Salmonella have been cultivated from cockroaches obtained from sewer manholes.[222] Fish living in polluted water may harbor Shigella and Salmonella. After fish are caught, these bacilli may reach the flesh, which then may serve as a source of disease in humans.[223]

Shigellosis.—Felsen and Wolarsky believe bacillary dysentery to be increasing rapidly in incidence in the United States. Yet there is no reason why it should, and Federal statistics show a decrease.[224] The authors long have felt that bacillary dysentery is the primary cause of ulcerative colitis but, again, without convincing evidence to support their view.[225]

Food Poisoning.—Roasted pork containing heat-resistant Clostridium welchii poisoned 44 persons. Symptoms lasting a day were confined to the colon without vomiting or fever. They began 8 to 16 hours after eating pork which had been cooked the day before.[226] Failure in experiments to cause illness by feeding four strains of C. perfringens and four strains of Bacillus cereus to volunteers does not exculpate these bacteria.[227] Experiments of Shaughnessy may be recalled wherein ingestion of Shigella often failed to cause dysentery. Evidently other factors in addition to the presence of potential pathogens are needed before disease occurs. Parker has described the diagnosis and management of outbreaks of food poisoning on shipboard when diagnostic laboratory facilities or other aid are not available.[228]

Other Diarrheal Diseases.—Diarrhea in infancy often is caused by unknown agents, in many cases probably by viruses. Certain varieties of colon bacilli may be pathogenic for infants. Therapy with broad-spectrum antibiotics may be effective.[229] One wonders if in certain instances these colon bacilli are merely commensals. In the case of hog cholera, Salmonella once was thought to be the cause, but a virus is the pathogen. An epidemic of diarrheal disease, probably viral dysentery, involved over 3000 persons in Japan in the spring of 1948. A few aged patients died. Volunteers who ingested filtered samples of stools from victims developed diarrhea. After a short interval, attempts to reinfect them failed, probably because of acquired immunity.[230] An epidemic of 46 cases of winter vomiting disease was observed in England.[231]

Bacillary Bacteremias.—Sixty-five cases of bacteremia with colon-bacilli have been studied. They are the commonest Gram-negative bacillary invaders. The genitourinary tract was the portal of entry in 60%; the gastro-

intestinal tract and biliary passages, in 30%. Over 75% of patients were more than 50 years of age. Combined therapy with a tetracyline antibiotic and streptomycin is the treatment of choice. The mortality rate is 10%.[232]

Similar study has been made of 20 cases of bacteremia with Aerobacter aerogenes over a 14-year period. Of these, 17 were in patients over 40 years of age and in 15 the urinary tract was the portal of entry. Streptomycin combined with tetracycline was used in therapy, which was not particularly satisfactory.[233]

In 10 patients with bacteremia caused by P. aeruginosa (Bacillus pyocyaneus) the portal of entry in most, as in the two preceding infections, was in the urinary tract. Three died. Each of three who received polymixin B sulfate recovered. The recommended dose is 100 to 200 mg. intramuscularly in four doses for adults. The drug should be used for treatment only in this infection. It is toxic.[234]

Other Bacillary Infections.—Contamination of the spinal fluid during lumbar puncture may cause meningitis. P. aeruginosa is an important invader. The infection may be prolonged and often is fatal. Several "cures" have been reported after therapy with a variety of broad-spectrum antibiotics.[235] Meningitis has been caused experimentally by inoculating monkeys intraspinally with P. aeruginosa mixed in jellied agar. Inoculated pneumococci and E. coli, but not viridans streptococci, also caused meningitis.[236]
had been reactivated by surgery.

During the period of shock in cholera, the kidney shows evidence of incomplete and patchy cortical ischemia. It probably is caused by a reduced flow of viscid blood and cortical vasospasm. The parenchyma usually is unharmed.[237]

A pertussis-like disease caused by a bacillus different from B. pertussis is newly recognized as an entity. Unfortunately, it was given an undesirable name—parapertussis. It is milder than whooping cough. Specific antibodies were demonstrated in 76% of sick children. An epidemic of 5000 cases occurred in Denmark in 1950-1951. It is said to occur also in the United States.[238]

Evidence incriminates a newly recognized, fastidious, pleomorphic, Gram-negative bacillus as the cause of nonspecific bacterial vaginitis. It belongs in the genus Hemophilus.[239]

DISEASES CAUSED BY COCCI

Hemolytic Streptococci.—Therapy of scarlet fever with penicillin usually prevents bacterial invasion of other tissues, but the incidence of toxic complications is only slightly reduced. The period of hospitalization is about one week for treated patients and six weeks for untreated ones.[240] Scarlet fever patients treated with penicillin give rise to far fewer contact infections in their families or in hospital wards than untreated ones. Parenteral therapy is better than oral therapy. As an epidemiologic measure, patients suspected of having scarlet fever, carriers of hemolytic streptococci, and persons in contact with patients should be treated with penicillin.[241]

In a four-year study, hemolytic streptococcosis in young children has been found often to be mild or inapparent. Its more severe form has a gradual onset and a long course. The infection can be terminated with penicillin. In children over 4 years old, the pattern is different. The onset is more abrupt, with sore throat and occasionally a rash. Rheumatic fever may follow. The nature of the disease in older children probably is due to repeated infection earlier in life and a consequent change in the response to reinfection.[242]

Wilmers and her co-workers isolated Type 12 hemolytic streptococci from almost all of 31 patients with acute glomerulonephritis. Type 12 streptococci are encountered often in England and are an important cause of nephritis.[243] Inoculation of Type 12 streptococci repeatedly over long periods in rabbits does not cause nephritis or any lesions resembling those of rheumatic fever.[244]

A form of nephropathia epidemica has been observed in Scandinavia since 1933. Because it is not preceded by any obvious in-

fection and there is no edema or hypertension, it is believed to be an entity different from the usual form of acute nephritis. Recovery is the rule. A viral agent is suspected as the cause.‡ No mention has been made of efforts to isolate possible causative streptococci.

By adding penicillin and an appropriate amount of electrolyte to culture media, strains of hemolytic streptococci gave rise to so-called L forms. The biologic significance of these forms is unknown, but they may be important as the cause of the obscure pathogenic action of streptococci in certain diseases.[248]

Rheumatic Fever.—In a Milroy lecture, Long reviews knowledge of the pathogenesis of rheumatic fever in the light of recent advances and proposes a new complicated theory.[249]

Rheumatic fever, as is well-known, is less serious if it begins in adult life. In a study of 98 veterans whose first attack occurred during military service, residual cardiac disease developed in about 18%. Of these, almost all were gainfully employed four to eight years later.[250] Several cases of active rheumatic fever have been observed in patients over 60 years old. At that age, the symptoms are uncharacteristic.[251]

Studies of left auricular appendages removed at operation from 183 patients with mitral stenosis revealed Aschoff bodies in 45%. They were present in 73% of patients under 30 and in 8% of those over 50 years of age. If these bodies indicate low-grade infection or active inapparent rheumatic disease, none of the tests usually applied such as measurement of the sedimentation rate, the antistreptolysin-O titer, and electrocardiography had given any evidence of it.[252] Of 179 other patients subjected to mitral commissurotomy, 67 had recurrent pain in the chest, and in 43 a febrile illness resembling rheumatic fever occurred, as if the disease had been reactivated by surgery.[253]

The relative merits of cortisone and salicylates separately or combined in the treatment of rheumatic fever have been tested. English clinicians gave both drugs to patients and believe that their combination is more effective than either drug used alone. The sedimentation rate reached normal in an average of 17 days as compared with 39 days in patients who received salicylates. There was a corresponding rapid improvement in the clinical condition.[254]

Benzathine penicillin G, a long-acting repository preparation, was given once every four weeks in doses of 1,200,000 units (720 mg.) intramuscularly to 96 children who had or had had rheumatic fever. During therapy hemolytic streptococci were detected in only 4% of 1000 cultures. There were no clinical recurrences of rheumatic fever.[255]

A symposium of nine papers appeared in the December, 1954, issue of the *American Journal of Medicine*. Eradication of Group A streptococci seems to be the most important factor in preventing rheumatic fever. For this purpose, sulfonamide compounds should never be used (Catanzaro). Penicillin is the drug of choice. To avoid unnecessary therapy in patients with viral or nonstreptococcic sore throat, the clinical criteria for diagnosing streptococcic sore throat should be more widely known. Sudden onset, bright red inflammation, pharyngeal exudate, cervical adenitis, fever, and leucocytosis are characteristic. Preceeding streptococcic infection was inapparent in 38% of patients who developed rheumatic fever. In these there is no way known at present to prevent the disease (Stollerman). C-reactive protein antiserum is available commercially. C-reactive protein always is demonstrable during rheumatic fever, and the amount present is often in proportion to the severity of the disease. Its disappearance indicates recovery from infection (Wood). Criteria for the selection of patients for mitral commissurotomy have been outlined by Zinsser. Ten days to 7 months after operation 10% to 30% of patients develop pain in the chest, fever, cough, hemoptysis, and arthralgia known as the postcommissurotomy syndrome. The cause is unknown (Elster). As mentioned in a previous paragraph, others regard the cause as a recurrence of rheumatic fever.

‡ References 245-247.

Endocarditis.—Of 52 cases of subacute bacterial endocarditis, about one-third of those considered cured by antibiotic therapy died later of congestive heart failure, one-third are alive but disabled, and only 23% are without symptoms or disability. The authors recommend prompt and thorough treatment when the disease is suspected.[256] According to Bunn and Cook, the method of therapy has not been improved in recent years. Of their 48 patients, 31% died. The chief causes of death were antibiotic-resistant bacteria, insufficient therapy, and irreversible heart failure.[257] Experimental bacterial endocarditis with lesions resembling those seen in humans was caused by inoculating S. faecalis into mice kept in low atmospheric pressure. Injection of penicillin brought about regression of the lesions, but bacteria remained inside of macrophages and were relatively resistant to penicillin. This may explain failure of therapy at times in human cases and why recurrences take place after inadequate treatment.[258]

The third case of endocarditis in the United States caused by Micrococcus tetragenus has been described. Despite large doses of penicillin with probenecid (Benemid), chloramphenicol, and bacitracin, the patient died. At necropsy, colonies of the cocci were seen in sections of leaflets of the mitral valve.[259]

Staphylococci, as in the case of hemolytic streptococci, were found to cause various kinds of disease in members of nine families. Person-to-person infection with single phage types of cocci occurred and caused styes, boils, suppurative arthritis, and osteomyelitis. The nasal carrier rate in normal persons is between 27% and 47%, and in patients with boils, 68%. Twenty-three per cent of staphylococci, mostly of Group 1, are resistant to penicillin.[260] Attempts at suppression of dust have failed to control the spread of penicillin-resistant staphylococci in hospital wards. Apparently infection is spread by contact, not by airborne cocci.[261] Penicillin-resistant staphylococci are discussed on a previous page.

DISEASES CAUSED BY FUNGI

Histoplasmosis.—Loosli made a three-year study of six members of a family who probably were infected while working in a silo in which H. capsulatum was present. The victims had disease in different degrees of severity. As each one recovered, the complement-fixation test became negative but the histoplasmin skin test stayed positive. The pulmonary lesions healed by fibrosis and calcification.[262] Sutliff and his co-workers observed four cases of chronic active pulmonary histoplasmosis. The disease strongly resembled tuberculosis, with lesions in the upper lobes and cavitation. Diagnosis may be made by finding H. capsulatum in the sputum or in resected pulmonary tissue. The course is benign, and there is no specific therapy.[263] Prior described several cases in Ohio. Two had chronic, low-grade pulmonary disease and recovered. One had fulminating pneumonia, and diagnosis was made at necropsy.[264] A case of acute, multifocal pulmonary histoplasmosis with recovery was observed in which infection came from inhaling dust while sifting garden soil.[265] Soucheray had three cases of "farmer's lung," probably also a mycotic disease contracted by inhaling moldy dust.[266]

Histoplasmosis may occur in nonendemic regions in persons who have previously resided in endemic ones.[267] The fungus is found naturally not only in soil but also floating in the air.§ In several instances, it was cultivated from the air of chicken coops in which persons were infected and from the open air.[270] The restriction of histoplasmosis to limited regions may be related to the nature of the soil. Red-yellow podzolic soils seem to be most favorable for the fungus.[271] H. capsulatum has survived in tap water at 4 C for 621 days and at 20 C for 550 days. It has resisted freezing and thawing for 198 days.[272]

After Darling discovered histoplasmosis in Panama in 1906, no cases were reported from there until 1945. Many, no doubt, had

§ References 268 and 269.

occurred unrecognized. Zimmerman described a case studied at necropsy in 1931. Study of surgically removed pulmonary lesions revealed Histoplasma in 13 patients who had lived in Panama.[278]

The second case of disseminated histoplasmosis has been observed in England. The patient had been in Africa and India before 1945. Three other patients with localized histoplasmosis had lived in India.[274] A case in a native in Nigeria was caused by a new variety, Histoplasma duboisii. There were extensive dermal lesions first suspected as leprotic.[275] Ten natives in Uganda reacted to the histoplasmin skin test.[276]

Histoplasmosis occasionally is discovered during mass roentgenographic surveys. Forsee excised pulmonary lesions in 30 patients and demonstrated the fungus in sections of tissue. They were cultivated from only one specimen. The lesions, often solitary, may persist harmlessly for years. They resemble tuberculomas and coccidioidomas.[277]

Dogs may be infected experimentally with the yeast phase of H. capsulatum inoculated intratracheally but not by feeding. The fungus in its mycelial phase failed to cause infection unless the dogs had been given cortisone beforehand.[278] In other studies, 102 of 5000 dogs tested in Ohio reacted to the histoplasmin skin test. Sixty-two of these had active histoplasmosis, chiefly of the pulmonary or gastrointestinal tract. Histoplasma organisms were excreted in the sputum, urine, feces, saliva, and vomitus. Study of 68 persons intimately exposed to histoplasmic dogs and of 42 laboratory workers who were exposed to infection for five years did not reveal evidence of infection. In Virginia, H. capsulatum was isolated from the lymph nodes of 22 of 50 cats and from the same numbers of dogs. There was systemic dissemination in nine, but the animals seemed to be well.[279]

Fungicidin (Mystatin) reduced the mortality rate when given to mice infected with H. capsulatum.[280]

Coccidioidomycosis.—According to Forsee, about 2% of patients with coccidioidomycosis develop a solid or cavitary pulmonary lesion. It usually is discrete, up to 3 cm. in diameter, and in the upper lobes. From experience with 50 cases, he feels that surgical extirpation is the best form of treatment.[281] Coccidioidomycosis and tuberculosis both were active in 24 patients. Nine patients with pulmonary cavities were treated successfully by resection.[282] In another series of 35 surgically resected pulmonary granulomas, tubercle bacilli were found in 6, Coccidioides in 3, and Histoplasma in 19. In seven no micro-organisms were demonstrable. Diagnosis in such circumstances is important for the selection of proper therapy.[283]

Malaria.—Seven papers in the November, 1953, issue of the *American Journal of Tropical Medicine* attest to the value of primaquine in the treatment of malaria. Many studies were made in Korea on soldiers whose symptoms were suppressed by chloroquine but who developed acute attacks when they returned to the United States. In the summer of 1951, over 3000 cases were studied. Vivax malaria contracted in tropical regions caused clinical episodes at frequent intervals during the year. Malaria contracted in the temperate zone had a bimodal pattern, with a long interval between the first infection and/or attack and the first relapse, which occurred the next summer. Korean vivax malaria ends spontaneously within two years if no reinfection occurs.

According to Hall's experience the problem of treatment of Korean vivax malaria is almost solved. The administration of chloroquine phosphate for 2 days, followed by primaquine diphosphate for 14 days, at present, is the method of choice. Relapse rarely occurs. He points out that in 35% of cases the attacks were not so typical as described in textbooks and many erroneous diagnoses and unnecessary laboratory tests are made.[284]

An unusual opportunity arose to study an outbreak of 34 cases of malaria in a nonimmune population in a nonendemic area. A veteran from Korea who had a relapse of malaria brought the disease into a group of 1800 persons in a vacation camp in Cali-

fornia. Mosquitoes obviously spread the infection after July 10. In nine victims, the incubation period was from 12 to 38 days, but in 25 the first illness was delayed until the next spring. In these the "incubation" period ranged from 226 to 307 days. Obviously, malaria may be latent for eight or nine months.[285]

Hepatitis, it is said, should be regarded as a significant feature of malaria and not as a complication. In 54 patients, the results of hepatic function tests were abnormal in 52. Biopsy of the liver revealed pathologic changes in 31.[286]

Toxoplasmosis.—In the United States, 20% to 40% of adults studied gave serologic evidence of past or present infection with Toxoplasma. While the mode of transmission of infection between man and animals is unknown, the feeding habits of the animals involved seem to be similar to those responsible for trichinosis. Evidence of infection between swine and rodents and in pigs from eating swine offal has been reported. The risk of infection of humans from eating poorly cooked or raw infected pork is undetermined.[287] Observations on human toxoplasmosis occurring coincidently with the disease in dogs further suggests direct infection from animal to man. The presence of Toxoplasma in the lungs, stomach, intestine, and kidneys of sick dogs renders their sputum, saliva, vomitus, feces, and urine potential transmitters of infection. Serum from 9 to 37 persons in contact with sick dogs had antibody against Toxoplasma.[288]

Toxoplasmosis may occur in different forms as an inapparent infection or a grippe-like disease. It may resemble infectious mononucleosis, cause chorioretinitis, or resemble a systemic infection or congenital disease.[289] Cases of encephalitis, chronic pneumonia, and asymptomatic toxoplasmic parasitemia have been described.[290] Toxoplasma was isolated from the blood and saliva of a child of 5 with nothing more than enlarged cervical lymph nodes.[291] Benign toxoplasmosis was described in a woman in whose blood a positive serologic reaction was demonstrated, and Toxoplasma organisms were seen in an excised lymph node. After subsequent pregnancy a normal infant was born. Serum of the infant gave a high titer in the serum-dye test.[292]

In the hands of Awad, the Feldman-Sabin dye-test for toxoplasmosis was found not to be specific. Cross reactions occurred with the serum of animals infected with Trichomonas vaginalis and Trypanosoma cruzi. Previous reports of epidemologic studies based on this test, in his opinion, must be regarded with uncertainty.[293] In an electron microscope study, structures were revealed in Toxoplasma organisms which have no known counterpart in other protists. This difference seems to set Toxoplasma apart, at present, from Encephalitozoan, Histoplasma, and other parasites.[294]

Pulmonary Disease.—According to editorial comment, none of the available antibiotics or sulfonamide compounds is suitable for the prolonged treatment of chronic bronchitis or bronchiectasis. Dangerous side-effects or the emergence of resistant varieties of bacteria may occur. Even if the ideal antibiotic were to be used, it is "clear that the diminution of bacterial infections will not always, perhaps not even very often, lead to more than slight or transient relief of the chronic symptoms".[295]

A fatal case of pulmonary fibrosis caused by a chronic granulomatous process in the parenchyma has been studied at biopsy and necropsy. Histoplasmosis was suspected, but cultures were unrevealing.[296] In 32 cases, roentgenography revealed mediastinal masses which proved to be either caseous, fibrotic, cystic, or calcified. Bacteriologic study failed to reveal the cause in any.[297]

Reports from two groups of observers cite the presence of Pneumocystis carinii, a protozoan, in the pulmonary tissue of 33 cases of interstitial plasma-cell pneumonia in infants.|| In a surprisingly large number of 66 cases of this unusual form of pneumonia, serologic evidence was said to confirm the causative role of the parasite.[300] More study is needed before acceptance of this view. Should the organism prove to be the

|| References 298 and 299.

cause, a new entity must be recognized. A case of pulmonary acariasis, usually thought to be a tropical disease, was observed in Spain. It had a prolonged course and eosinophilia.[301]

Cortisone and Infection.—In general, therapy with cortisone has a harmful effect during infectious disease, but, in certain cases, depending on the dosage, cortisone combined with antibiotic agents gives good results. In mice, cortisone impairs the effectiveness of all antibiotics except penicillin for three to six days. It has no restrictive effect on the protective action of penicillin in strepococcic infections in mice.[302] In other studies, cortisone rendered mice less resistant to infection with pneumococci and influenza virus. Pituitary adrenocorticotropin did not have that effect, and growth hormone (somatotropic hormone) did not increase resistance to infection.[303] Roentgen irradiation and cortisone separately or together decrease resistance to infections by injuring the mechanism of resistance.[304] According to editorial comment, cortisone tends to increase the susceptibility of vertebrates to almost all infections, whether of bacterial, treponemal, viral, fungal, or protozoal origin. There is no satisfactory explanation as to how or why. It has no direct effect on the pathogens and no significant effect on the polymorphonuclear leucocytes, and suppression of antibodies cannot wholly be accountable. It is unlikely that interference with complement or preformed antibodies is important. Perhaps one reason is an effect on the reticuloendothelial system akin to experimental blocking. A combination of several factors or something entirely unknown may be responsible.[305]

Clinical Use of Cortisone.—If, in severe cases, infection is adequately controlled by antibiotics, cortisone may be helpful in relieving symptoms. It has been used successfully in typhoid, brucellosis, and tuberculous meningitis.[305] Cortisone is recommended in pediatric practice together with antibiotic therapy only for the treatment of overwhelming infections. It may be given for periods up to a week. Perhaps a suppression of the intensity of the inflammatory reaction is helpful to recovery.[306] On the other hand, two patients who received cortisone for arthritis developed fatal fulminating pneumonia. The drug masked clinical evidence of infection.[307] In six other patients, cortisone or corticotropin caused dissemination of exudative dermatitis and staphylococcic bacteremia. One died. The hazard of lowered resistance to infection caused by cortisone far outweighs any transient advantage in certain nonfatal dermal diseases.[308]

Agammaglobulinemia.—Interest and diverse opinion have arisen in the rare condition agammaglobulinemia and its relation to infection. According to some observers, it is responsible for recurrent bacterial infections, for an absence of acquired antibodies, and for failure of antibiotic therapy. The injection of gamma globulin is said to correct the deficiency and restore the normal response to infection.¶ Another observer was unable to show a relation between a lack of globulins and unusual susceptibility to infection. Antibodies developed as usual in response to antigens.[311] Zinnaman recognizes two forms of agammaglobulinemia, one idiopathic or congenital, the other acquired or secondary to some disease of the reticuloendothelial system. In one case, no plasma cells were seen in specimens of spleen and a lymph node. Replacement of gamma globulin by injection did not restore resistance to infection. Continuous administration of antibiotics may prevent some infections but may favor others.[312] In Moncke's case, antityphoid vaccine caused an increase in the agglutinin titer.[313] Injected gamma globulin vanished after eight days.[314]

Neither do deficiency of diet and hypoproteinemia always cause a lack of immune response, as many believe. Antibodies have been evoked against diphtheria toxin in severely wounded malnourished soldiers with hypoalbuminemia as well as in normal control subjects.[315] In other studies, phagocytosis by neutrophilic cells is the same whether the cells are obtained from normal or from mal-

¶ References 309 and 310.

nourished persons. The number of leucocytes may be unchanged by prolonged starvation.[316]

MISCELLANEOUS ITEMS

Appendicitis.—According to Castleton, the fundamental principles involved in the treatment of acute appendicitis have not changed despite the use of antibiotics. The prevention and treatment of complications are aided by therapy with antibiotics and sulfonamide compounds, but obstruction must be relieved surgically. Undiagnosed abdominal disease should not be treated with antibiotics.[317] Although the death rate from appendicitis among policy holders of a life insurance company dropped by three-fourths in the past decade, the reduction was not wholly due to the effect of antibiotic therapy.[318]

Rickettsioses.—Broad-spectrum antibiotics in doses of 50 to 60 mg. per kilogram of body weight are curative for various rickettsioses. Of 588 patients with scrub typhus, who were adequately treated, none died.[319] Rickettsialpox, once thought to be limited to the vicinity of New York City, occurs in Africa. As shown on a world map prepared by the American Geographic Society of New York, evidence of rickettsialpox has been found in rodents in Korea. The Rickettsia of Rocky Mountain spotted fever have been discovered in meadow mice. They also reside in rodents in South America.[320] Naturally infected animals had never been reported before. In experiments with Rickettsia, the phenomenon of "interference" can not be explained by competition for the same cell hosts and subsequent exclusion of the challenging infection. Neither can saturation of susceptible cells by the first pathogen be credited. Interference seems to be due to a component of the primary invader.[321]

Pleuropneumonia Micro-Organisms.—At an international congress, Klieneberger summarized knowledge of this puzzling group of micro-organisms. They are not bacteria, viruses, mycetaceae, or asterococci. They undoubtedly cause disease in cattle, goats, rats, and mice, but only if the animal's resistance is lowered by other factors. The mode of their natural transmission is unknown.[322] Pleuropneumonia-like organisms (PPLO) resembling those associated with a serious epizootic pneumonia of cattle have been isolated from the pneumonic lungs of calves. Bacteria were present also.[323] PPLO may infect the genital tract of humans, but only if abetted by other factors. They may cause nonspecific urethritis. They were present in 80% of a group of women who had gonorrhea. Erythromycin, in one study, controlled gonorrhea but had no effect on PPLO.[324]

Syphilis.—Because of the present successful control of syphilis, a medical journal devoted to the disease has been discontinued because of lack of material for publication. Cutler and his associates inoculated 60 volunteers intracutaneously with T. pallidum. Eight who had not had syphilis before reacted in a manner characteristic of acquired infection. Of those who had had syphilis, 20 showed no clinical or serologic response. The degree of acquired immunity seemed to be related to the duration of the original infection before its treatment.[325] The development of the treponemal immobilization (TPI) test by Nelson in 1948 is said to be the most important advance in diagnosis since the introduction of the complement-fixation test. The TPI test is specific for syphilis, yaws, pinta, and bejel but does not differentiate them. Since syphilis alone is of importance in the United States, the test is of value in diagnostic problems involving biologic false positive reactions to the standard serologic tests. Reaction to the TPI test probably persists for life if the patient is not treated early in the disease.[326] Technique similar to that of the TPI test is said to be useful in the diagnosis of amebiasis and schistosomiasis.[327]

Leptospirosis.—L. ballum was discovered in house mice and in an opossum during an investigation of animal carriers in an endemic region of Virginia.[328] L. pomona has not been found in rodents and probably is restricted to livestock. L. pomona is a frequent cause of disease in cattle and hogs in Iowa. Samples of blood from 140 veteri-

narians gave positive agglutination reactions for L. pomona and L. canicola.[329]

In 1942, three groups of persons who bathed in swimming pools in Idaho and Wyoming developed illness diagnosed as typhoid. Subsequent study of some of the victims 11 years later revealed antibodies in their blood specific for L. canicola. The disease they had probably was leptospirosis.[330]

Schistosomiasis.—Twenty-six Puerto Rican soldiers in Germany who had passed the induction physical examination were admitted to military hospitals for various reasons. On study all were found to be infected with S. mansoni. Ova were present in feces or were found in specimens of rectal and hepatic tissue removed at biopsy. Treatment with potassium antimony tartrate often caused toxic symptoms and eosinophilia.[331]

Katayama disease in one case was said to be the severe toxemic stage of schistosomiasis mansoni. The patient, a child, began to vomit and have fever, cough, and rales 26 days after infection. There were diffuse miliary shadows in the lungs and eosinophilia as in Loeffler's syndrome.[332] Increasing knowledge of the primary severe reaction to parasitic disease renders the use of eponyms unnecessary.

Trichinosis.—Eighty-two cases of trichinosis, of which 60 were in women, were observed in Liverpool. Many were sick for four to six weeks. Infection was traced to sausage.[333] Five papers presented at a National Conference on Trichinosis appeared in the Aug. 14, 1954, issue of *The Journal of the American Medical Association.* They dealt chiefly with methods of prevention. The most effective measures seem to be feeding cooked garbage to hogs and the quick "deep" freezing of pork. Specific recommendations are given in detail. Gould and his co-workers showed how trichinous pork can be sterilized by exposure to Co^{60}. The exposure of all raw pork to gamma radiation of waste products of fission may be a practicable way of controlling trichinosis.[334]

Administration of adrenocorticotropin to rats infected with T. spiralis caused a depression of eosinophilia and a change in the inflammatory response, but it had no particular therapeutic influence.[335]

Amebiasis.—The inhabitants of a Japanese village were treated with carbarsone and chiniofon in successive weeks. The incidence of carriers of E. histolytica was reduced from about 50% to 3.8% when examinations were made after seven months. By that time, some persons probably were reinfected.[336]

Vaccination Sequels.—Neurologic disorders in the form of radiculitis, polyneuritis, myelitis, the Guillain-Barré syndrome, and others may follow vaccination against tetanus, typhoid, pertussis, diphtheria, and rabies. The nervous system may be affected at any level. Anaphylactic hypersensitivity may be a causative factor.[337]

Other Studies.—In performing experiments on rabbits, investigators should be familiar with the natural diseases of the animals to avoid misleading observations. In one study, nearly a third of 900 rabbits had a naturally occurring mild chronic infection.[338]

Pillemer isolated a new serum protein, properdin, which may play an important unspecific role in natural immunity and in defense against infection. It apparently can be destroyed by total body irradiation. When reinjected into irradiated rats, it gave partial protection against infection.[339]

Burnet has discussed newer aspects of immunity in which heredity and development play significant roles. Cells concerned with immunity react differently to foreign substances during intrauterine life than afterward. Fetal cells exposed to infectious agents, for example, lymphocytic choriomeningitis or hepatitis, become permanently tolerant to them. In later life, the same cells become antagonistic and produce specific antibodies.#

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ADDENDUM

Six immunologic types of a newly isolated virus called APC (adenoid-pharyngeal-conjunctival) have been isolated from patients with colds. Virus of Type 3 causes acute nasopharyngitis; Type 4 causes acute respiratory disease and viral pneumonia (Respiratory System Viruses, Conference Report, *Pub. Health Rep.* **70**:207-209 [Feb.] 1955). A "new" disease called pharyngoconjunctival fever is caused by virus Type 3 (Bell, J. A., and others: Pharyngoconjunctival Fever: Epidemiological Studies of a Recently Recognized Disease Entity, *J. A. M. A.* **157**:1083-1092 [March 26] 1955).

Case Reports

HEMOGLOBIN-C DISEASE

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BY THE USE of filter-paper electrophoresis, the hematologist has gained a relatively simple and accurate method of differentiating the various abnormal or atypical hemoglobins.* Thus, we may identify normal hemoglobin (A), sickle hemoglobin (S), the combination of these (S-A) and C-hemoglobin in its homozygous (C-C) and heterozygous (C-A, C-S) states. From a practical standpoint, anemias which previously were undiagnosed or considered to be atypical sickle-cell anemia may be recognized now. It is the purpose of this paper to add to the literature another case of homozygous hemoglobin-C disease which was of particular interest because of the relatively long documented course of the illness, which prior to paper electrophoresis had been undiagnosed. The patient was followed intermittently from 1948 (when she first presented herself for treatment, with symptoms suggestive of gall-bladder disease) to 1953, when the syndrome was recognized and confirmed by paper electrophoresis.

METHOD OF ELECTROPHORESIS

A small tank was constructed of methacrylate (Plexiglas) (Fig. 1). The dimensions (5 by 8 by 2 in.) are not critical. Each of the two chambers of the tank is filled with 150 to 200 ml. of barbital (Veronal) buffer (pH 8.6). Platinum foil electrodes are placed in opposite corners of the tank and the source of direct current applied to them when desired by use of spring clamps.

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* References 1-3.

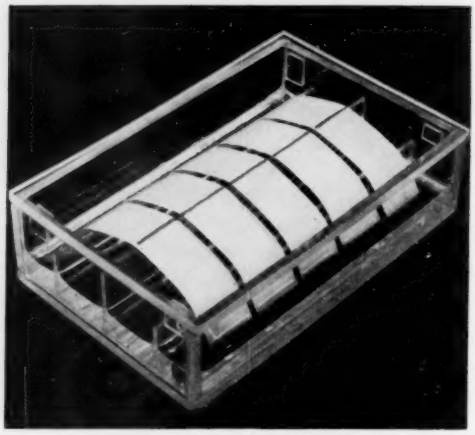
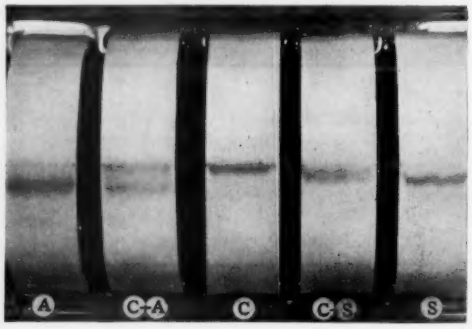


Fig. 1.—Methacrylate (Plexiglas) tank used for electrophoresis in this study. The ends of the filter paper strips dip into the buffer in each compartment. Electrodes are placed in opposite corners. Other details are given in the text.

Sheets of Whatman No. 3 filter paper are cut into 1 by 5 in. pieces. Prior to use these are gently bent in the middle by pressing over a glass rod. A 3% to 10% hemoglobin solution, 0.01 ml., prepared by the method of Singer and co-workers,[4] is applied across the center of the strip. The procedure can best be accomplished by holding the capillary pipette, containing the solution, as a pencil and applying it across the paper with steady, light pressure.

The strips are placed in the tank as seen in Figure 1. Buffer will rise to the apex of each by capillary action. This may be hastened by wetting evenly both sides of the paper strip with buffer from a

Fig. 2.—Hemoglobin migration observed at two hours. From left to right: A, C-A, C (patient), C-S, S hemoglobin. Note that the C-hemoglobin has barely moved from the origin (center).



pipette. The tank is covered to maintain adequate humidity within. Good hemoglobin migration is obtained when a potential difference of 160 volts is applied to the electrodes over a 2- to 4-hour period.

It is advisable to determine the results before the procedure is terminated. Thus the various hemoglobin bands will be observed at a time when they are most distinct (Fig. 2). When the process is completed, the paper strips may be dried in an oven for 5 to 10 minutes. This reduces blurring of the hemoglobin lines. If so desired, the strips may be stained as described by Larson and Ranney.[5]

REPORT OF CASE

The patient was first seen in the outpatient dispensary on April 20, 1948. She gave the history of having had a feeling of fullness in the chest and epigastrium following meals since October, 1947. She also complained of a dull ache in the left side radiating to the back and mainly associated with eating fatty and fried foods, milk, and cooked white potatoes. She had lost an unknown amount of weight.

Family History.—The patient knew nothing of her father, and her mother died at the age of 56 of pneumonia. There were three siblings who died of unknown causes. She has three sisters, living and well, in another city. One sister has C-A hemoglobin, with target cells on smear but no anemia. To date we have been unable to study the other two or their children. The remainder of the history is not pertinent.

Past History.—From 1929 to 1931, the patient had occasional aches in various joints and was told that she had rheumatism. However, there had been no swelling, redness, or heat of the involved joints. In 1940 she had a hysterectomy and some time shortly after, an episode of jaundice which lasted an unknown period of time.

Menses.—Prior to the hysterectomy, the menstrual periods occurred at monthly intervals. The average duration was three days. She had never been pregnant.

Physical Examination.—The patient was a well-developed and well-nourished Negro woman who did not appear to be ill. A 7 mm. scar was present in the right lower quadrant. There was no lymphadenopathy or pallor. Neither abdominal organs or masses were palpated on her first visit to the clinic. The remainder of the examination was negative.

Course.—It was believed that the patient had chronic cholecystitis. On April 24, 1948, an oral cholecystogram was performed and the gall bladder was visualized with moderate concentration of dye. (X-ray studies performed in 1953 indicated a normally functioning gall bladder.) On May 4, 1948, x-ray studies of the gastrointestinal tract, including the small bowel, demonstrated a diverticulum at the cardia of the stomach. Blood cell counts are reported in Figure 3. Repeated occult blood studies of the stools were negative. On May 19, 1948, the spleen was first reported enlarged.

Following these initial visits, subsequent ones were sporadic. She first returned about a year later in April, 1949, complaining of pain in her left side and easy fatiguability. Results of liver-function studies are reported in the Table. She did not return to the clinic until two years later, July, 1951. She complained of pain in the left shoulder, weakness, and easy fatiguability for the previous four weeks. Her gastrointestinal complaints were minimal. Examination revealed pain with elevation of the left arm and the previously noted enlarged spleen. There was a moderate anemia, but splenomegaly was as yet unexplained. Gastric analysis revealed no free hydrochloric acid, with a decrease in total acid. Saline fragility was diminished, with

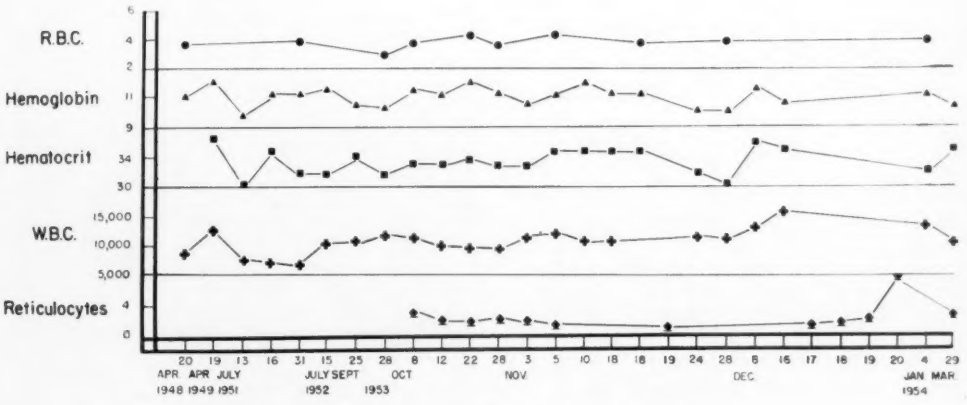


Fig. 3.—Blood cell counts during 1948 and 1954.

Laboratory Data

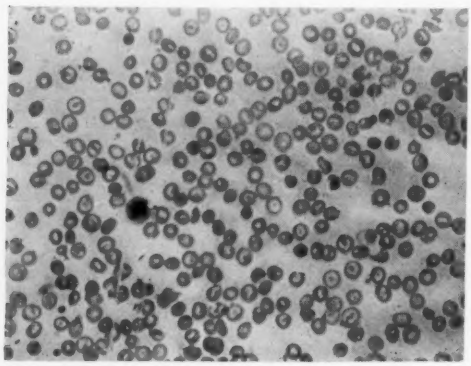
	4/18/49	8/20/51	8/13/52	9/28/53	11/9/53	11/18/53	11/24/53	12/4/53	12/6/53	12/7/53	12/16/53	12/17/53
Sulfobromophthalein retention	0	.....	...	....	...	0	....	.....	.....	.....	....	.....
Alkaline phosphatase, units	3.3	.....	...	....	...	5.6	....	.....	.....	.....	....	.....
Total protein, gm	6.3	.....	...	8.68	...	7.55	6.75	.....	.....	.....	8.10	.....
Albumin, gm	3.7	.....	...	4.76	...	4.05	3.78	.....	.....	.....	4.19	.....
Globulin, gm	2.6	.....	...	3.92	...	3.50	2.97	.....	.....	.....	3.91	.....
A/G ratio	1.4	.....	...	1.21	...	1.15	1.27	.....	.....	.....	1.07	.....
Kunkel globulin	...	.....	...	....	...	16.5	....	.....	.....	.....	....	.....
Cephalin flocculation												
24-hour	2+	.....	...	3+	...	4+	....	.....	.....	.....	....	.....
48-hour	3+	.....	...	4+	...	4+	....	.....	.....	.....	....	.....
Thymol turbidity, units	...	.....	...	4	...	3	....	.....	.....	.....	....	.....
Cholesterol, mg./100 cc	...	.....	...	....	...	176	....	.....	.....	.....	....	.....
Prothrombin time, sec. patient (control)	...	.....	...	....	...	....	18 (15)	21 (14)	19 (15)	16 (14)	....	.....
Bilirubin, mg./100 cc.												
Direct-reacting	...	.....	0.6	0	0	0	....	.....	.....	.....	....	.....
Indirect-reacting	...	.....	1.7	1.05	1.3	0.95	....	.....	.....	.....	....	.....
Fragility												
Patient	...	0.38-0.20	...	....	...	....	....	.....	.....	.....	....	0.40-0.24
Control	...	0.42-0.32	...	....	...	....	....	.....	.....	.....	....	0.42-0.36
Sickling	...	.....	Neg.	....	...	....	....	.....	.....	.....	....	.....
Urine urobilin	...	.....	1:40	....	...	....	....	.....	.....	.....	....	.....
BUN, mg./100 cc	...	.....	...	13.5	...	....	....	.....	.....	.....	....	.....

beginning hemolysis at 0.38% saline, complete at 0.20%, as compared with a control value of 0.42% to 0.32%.

The patient was not seen again until a year later, July, 1952. She then complained of pain in the region of the right iliac crest posteriorly with increase in pain with motion. She had no gastrointestinal symptoms. Physical examination revealed bilateral periorbital edema, and tenderness to palpation and movement of the right leg at the hip joint. X-ray studies of the abdomen revealed considerable enlargement of the spleen, with displacement of the left kidney downward and medially. A bone marrow study was done on Aug. 6, 1952, and was interpreted as follows: "The smears are moderately hypercellular with a WBC:RBC ratio of 1.2:1. The nucleated red blood cell series was markedly increased in number, with a shift to the left and an increase in basophilic forms. The normoblasts are smaller in size as seen in iron deficiency anemia. The erythrocytes show target cells and moderate achromia. The granulocytic series appears normal and platelets are adequate. Impression: Hyperplasia of red cells." Sickling preparations were negative. Urobilinogen in the urine was 1:40.

On Aug. 12, 1952, direct-reacting bilirubin was 0.6 mg. and indirect-reacting, 1.7 mg. per 100 cc. An intravenous pyelogram showed an ectopic kidney on the left. The patient's symptoms cleared, and she did not return to the clinic until September, 1953. At that time, she returned with her original complaints of pain and fullness after eating. Because of the unexplained anemia and splenomegaly, the patient was again subjected to a wide variety of studies. They are detailed in Figure 3 and in the Table; in summary, she showed mild anemia, increased indirect-reacting bilirubin, an abnormal cephalin-flocculation test, and otherwise normal liver-function tests. The patient improved with symptomatic care, but her anemia failed to respond to successive trials with iron and vitamin B_{12}.

Fig. 4.—Photomicrograph of peripheral blood smear. Note the presence of many target cells. Wright's stain.



She was then admitted to the George Washington University Hospital, since she could not be classified in the clinic. Physical examination revealed an enlarged spleen, 3 cm. below the costal margin. The cephalin-flocculation test was 4+. A liver biopsy was done Dec. 9, 1953, and was interpreted as showing normal liver. By this time, the combination of splenomegaly, reticulocytosis, hyperbilirubinemia, increased resistance to hypotonic saline, and the number of target cells in the peripheral smear (Fig. 4) plus a negative sickling reaction suggested hemoglobin-C disease. This diagnosis was confirmed when paper electrophoresis revealed homozygous hemoglobin C. The patient was discharged and has been followed in the clinic, where she has remained relatively symptom-free. She has continued to work as a domestic.

COMMENT

Our patient showed intermittent symptoms suggestive of gall-bladder disease, splenomegaly, mild anemia, elevation of the indirect-reacting bilirubin, reticulocytosis, numerous target cells, absent sickling, decreased osmotic fragility, and a normoblastic hyperplasia of the bone marrow. Paper electrophoresis revealed 100% hemoglobin C. Most of these characteristics were present in previously described cases.† In addition, our patient showed an increase in globulin, a positive cephalin-flocculation test, and some decrease in prothrombin concentration. It seems unlikely that these features are associated with her hemoglobin-C disease, but it would be interesting to see these tests repeated in other cases. Observation over the six years that this patient has been followed indicates that her hematological values have remained quite constant. There has been nothing suggestive of a crisis, and our case confirms the general impression that homozygous hemoglobin-C disease is a mild, relatively stable hemolytic anemia.

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News and Comment

ANNOUNCEMENTS

Graduate Medical Training in Neurology and Ophthalmology.—Graduate medical training grants of $126,000 have been awarded to the Graduate School of Medicine for a two-year period by the National Institute of Neurological Diseases and Blindness to initiate a unique program of training teachers and investigators in the fields of Neurology and Ophthalmology. Dr. Julius H. Comroe Jr., Professor of Physiology and Pharmacology, will be the program director.

The new course, to begin in the fall of 1955, will be the first of its kind in this country. It will be designed for neurologists and ophthalmologists who have decided to enter or continue a full-time academic career in teaching and research in these specialties. Prospective candidates must either be certified by the American Board of Neurology or the American Board of Ophthalmology or must have all or most of the requirements for Board certification. Preference will be given to men who have been selected by their own medical school faculties for advanced training, with the understanding that after the academic year at the Graduate School of Medicine they will return to their own departments to do full-time teaching and investigative work as a career. Probably not more than five neurologists and five ophthalmologists will be accepted during the first year; it is hoped that the majority of these will be able to obtain partial fellowship support during the training period. One or two internists or surgeons may be accepted during the first year in order to determine the effectiveness of the new program in training medical teachers and investigators in general.

An important part of this new course will be instruction in the art and technique of teaching. This will be accomplished largely by practical work. Initially, the group technique will be utilized, in which each member of a small group is in turn the lecturer while the remainder of the group serves as a critical audience. Each lecture will be recorded so that the lecturer will have the benefit of both the playback and the audience reaction (see *J. M. Education* **29**:39, 1954). Recordings will be kept and compared with later performances in order to gauge progress. Later, the "students" will be given active teaching responsibilities, under supervision. Since teaching involves more than lecturing to large groups, there will also be considerable practice in conference, seminar, and ward round types of teaching. No attempt will be made to achieve uniformity in teaching; the emphasis will be upon improvement in those teaching techniques best suited to the personal attributes of each physician. In addition, attention will be paid to the use of visual aids, the proper design of examinations, and appropriate faculty-student relationships. Special seminars on medical writing and library utilization will be given. The men will also be given broad training in the basic medical sciences of physiology, pharmacology, biochemistry, anatomy, pathology, and microbiology, with particular emphasis on their relation to clinical problems.

Another feature of the course will be a training program designed to provide a good scientific background for medical research. The Faculty realizes full well that it cannot create investigators by didactic courses. However, it believes that it can provide an opportunity for advanced learning that would be very difficult to obtain through existing means. Among the new courses to be created especially for this group are the following:

1. Mathematics for physicians engaged in medical research
2. Statistics and the design of experiments
3. Recent advances in electronics, chemistry, and physics
4. Techniques of investigation and their critical analysis
5. Seminars on critical evaluation of medical literature
6. Philosophy of research.

Since many of the trainees may eventually become departmental chairmen, special seminars will also be given on medical administration (including budgeting, personnel selection, hospital administration, and voluntary health plans).

These courses will be given by outstanding teachers, clinicians, scientists, editors, and educators, many of whom will be from universities outside of the Philadelphia area.

Although it is anticipated that "students" in this course will already be well qualified clinically, courses in the present program of the Graduate School of Medicine may be taken by the group as elective courses. In addition, an opportunity will be offered for investigative work. The course work, coupled with research, will be acceptable as credit for the degree of Doctor of Science (Med.). Address inquiries to J. H. Comroe Jr., M.D., Graduate School of Medicine, University of Pennsylvania, Philadelphia 4.

English and Spanish Summaries.—The *Deutsche medizinische Wochenschrift* has announced that it is now printing English and Spanish summaries of all original articles published in each issue in the hope that more lively exchange of medical information between English- and Spanish-speaking countries and Germany will result.

Course in Postgraduate Gastroenterology.—The American College of Gastroenterology announces that its Annual Course in Postgraduate Gastroenterology will be given at The Shoreland, in Chicago, on Oct. 27, 28, and 29, 1955.

The course will again be under the direction and co-chairmanship of Dr. Owen H. Wangensteen, Professor of Surgery of the University of Minnesota Medical School, who will serve as surgical coordinator, and Dr. I Snapper, Director of Medical Education, Beth-el Hospital, Brooklyn, who will serve as medical coordinator. Drs. Wangensteen and Snapper will be assisted by a distinguished faculty selected from the medical schools.

The subject matter to be covered in the course, from a medical as well as surgical viewpoint, will cover, essentially, the advances in diagnosis and treatment of gastrointestinal diseases and a comprehensive discussion of diseases of the mouth, esophagus, stomach, pancreas, spleen, liver and gallbladder, colon, and rectum, with special studies of radiology and gastroscopy.

For further information and enrollment write to the American College of Gastroenterology, Department P. G., 33 West 60th St., New York 23.

Minnesota Symposium on Arteriosclerosis.—The Minnesota Symposium on arteriosclerosis, sponsored by the University of Minnesota and the Minnesota Heart Association, will be held, Sept. 7-9, 1955, at Mayo Memorial, University of Minnesota Medical School, Minneapolis 14. For information, reservations, housing, etc., address Dr. Robert B. Howard, Mayo Memorial. Advance registration is desirable.

Five general sessions and a half-day of clinic and laboratory visits will be devoted to "The Challenge of Arteriosclerosis," "Atherosclerosis," "Peripheral and Cerebral Arteriosclerosis," "The Internist and Some Tools," and "The Surgical Treatment of Arteriosclerosis."

Speakers from outside Minnesota will include Drs. E. Cowles Andrus, Baltimore; C. B. Anfinson, Bethesda, Md.; Henry T. Bahnson, Baltimore; David P. Barr, New York; John F. Brock, Cape Town, South Africa; A. W. Duryee, New York; Miller Fisher, Boston; Charles A. Hufnagel, Washington, D. C.; Louis N. Katz, Chicago; Lena Lewis, Cleveland; Haqvin Malmros, Lund, Sweden; G. C. McMillan, Montreal, Canada; Elliot V. Newman, Nashville, Tenn.; M. F. Oliver, Edinburgh, Scotland; Irvine H. Page, Cleveland; T. Posteli, Bologna, Italy; Henry I. Russek, New York; Lester R. Sauvage, Seattle; William R. Scarborough, Baltimore; William P. Shepard, New York; Harris B. Shumaker Jr., Indianapolis; William B. Wartman, Chicago; James Watt, Bethesda, Md.; Edwin J. Wylie, Nürnberg, Germany.

Dr. Paul Dudley White, Boston, will speak on "The Coronaries Through the Ages" at the dinner meeting (Minneapolis Club) on Sept. 7.

Books

Needed Research in Health and Medical Care. By Cecil G. Sheps, M.D., and Eugene H. Taylor, M.D. Price, $5.00. Pp. 216, with 4 illustrations. University of North Carolina Press, Box 510, Chapel Hill, N. C., 1954.

A phenomenon of contemporary book publishing in this country is the appearance of stenotype reports of conferences, symposia, and colloquia. These are intended to give a view of the *status quo* and a preview of things to come. Their main usefulness has been in presenting an open discussion by workers in fast-moving technical fields. The book under consideration here indicates that such an approach is much less valuable when it attempts to forecast the direction which will be taken by the interdisciplinary approach to the less rigidly circumscribed fields of social sciences as they relate to medicine. The main difficulty for a novice in evaluating the usefulness of such an approach is difficulty in terminology. It is reasonable to hope that the intense interest and present confusion indicates darkness before the dawn and that out of this chaos will come a useful discipline encompassing many specialties. If the use of terms in a loose and slipshod fashion indicates a correlated looseness of thought, much tightening up is needed before we can hope to separate the strands of logic from those of mysticism. Someone will have to claw out the clichés and come down to brass tacks before it will be possible for the average interested physician or layman to get a clear view of what is proposed as well as what is already done in this field. The extremes to which confusion of thought can go might be illustrated by the reversion to primitive mythology expressed in a sentence like "I prefer to work with the concept of disease as an entity that is present or not present." In spite of the fact that this is a difficult and confusing book it indicates that there is active thought going on in an area which demands attention and which has promise of useful results.

Fat Metabolism: A Symposium on the Clinical and Biochemical Aspects of Fat Utilization in Health and Disease. Edited by Victor A. Najjar. Price, not given. Pp. 185, with 63 figures and tables. Johns Hopkins Press, Homewood, Baltimore 18, 1954.

Fat metabolism, which sometimes has been a neglected field of clinical and biochemical interests, has recently been making very rapid advances along several now converging, now separating lines. Better understanding of fat metabolism may shed useful light on America's increasingly heavy problem of obesity. Investigation into the still mysterious problems of arteriosclerosis and some of the metabolic derangements of diabetes is the best hope for light on problems which have not yielded their secrets so far.

Knowledge is advancing so rapidly that a symposium such as this is very useful to help the person not working on the subject to get a close view. This is especially helpful since the last few years have seen an extraordinary burst of success in experiments designed to unravel enzymatic mechanisms of fatty acid synthesis and oxidation. The outlines of the picture are now beginning to take definite, and perhaps definitive, form. The table of contents gives a diverse yet concise summary of these areas of most rapid advance. The contributors to the symposium have all made notable additions to our understanding. This book is recommended enthusiastically not only to those working in the laboratory but to clinicians interested in metabolic problems.

Liver Injury: Transaction of the Twelfth Conference. By F. W. Hoffbauer, M.D. Price, $4.25. Pp. 231, with 52 illustrations. Josiah Macy Jr., Foundation, 16 W. 46th St., New York 36, 1954.

This is a report of the Twelfth Conference on Liver Injury sponsored by the Josiah Macy, Jr., Foundation. Those persons interested in the liver and its diseases always eagerly await the report of this conference. This report is unusually good, covering broad subjects in the field.

One section is devoted to the liver and carbohydrate metabolism. In this section Dr. Einar Lundsgaard, of the department of physiology of the University of Copenhagen, Denmark, has set forth most interestingly the experience in his department with these problems. Dr. Joseph P. Hoet, of Louvain, Belgium, reported some very intriguing work that had to do with glycogen metabolism in the placenta and hormonal changes during pregnancy. The diabetogenic effect of pregnancy is discussed at length in relation to both animals and human beings, and this phase of the work will be particularly interesting to obstetricians and pediatricians.

The second section deals with the liver and fat metabolism by Samuel Gurin, of the University of Pennsylvania School of Medicine; the discussion on the liver and protein metabolism was led by Dr. H. W. Kosterlitz, of the department of physiology of the University of Aberdeen, Scotland.

This conference on liver injury continues to be an outstanding contribution, and although this particular report should be of great interest to those interested in the field of physiology and disease of the liver yet its implications would stimulate a much wider audience. It is worth while reading for any good internist.

The Pineal Gland: A Review of the Physiologic Literature. By Julian I. Kitay and Mark D. Altschule. Price, $5.00. Pp. 280, with 4 illustrations. Harvard University Press, Cambridge, Mass., 1954.

The authors are of the opinion that the pineal gland is not an inactive, vestigial structure but that it has functions which as yet are ill-defined. They contend that inadequate evaluation of published evidence is the reason that most investigators in this country consider the pineal gland to be functionless. The authors hope to rectify this situation by their book, which is a review of the world literature on studies of the pineal gland.

The book itself is short, containing only 280 pages, of which 164 are devoted to the bibliography. The text is divided into brief chapters dealing with a review of published data on the relationship between the pineal gland and the pituitary gland, gonads, adrenal cortex, thyroid glands, parathyroid glands, thymus, skin pigmentation, growth, development, and metabolism of various substances.

As the authors have noted, most of the published papers contain data too scanty to permit valid statistical evaluation. Hence, confirmation or denial of many of the proposed functions of the pineal gland must await further investigation. However, the published data, as reviewed by the authors, suggest that a definite relationship exists between the pineal gland and sexual development.

"The Pineal Gland" is a provocative book that will be of interest to endocrinologists and physiologists and should be a stimulus for new studies in this field.

Manual of Clinical Mycology. By N. F. Conant; D. T. Smith; R. D. Baker; J. L. Calloway, and D. S. Martin. Price, $6.50. Pp. 456, with 202 illustrations. W. B. Saunders Company, 218 W. Washington Sq. Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1954.

The necessity for making specific etiologic diagnoses in all infections came with the advent of sulfonamides and the present large variety of antibiotics, whose specific fields of therapeutic usefulness have now been well defined. It is now recognized that when antibiotic therapy directed against the easily recognized micro-organism in a lesion fails or even makes the infection more fulminating, search for one of the pathogenic mycotic agents must be made. Every physician must consider the possibility of their presence in obscure fevers, especially those associated with chronic lesions of the lungs, meninges, reticuloendothelial system, and skin.

Conant and his associates have attempted to put a usable guide for recognition of the fungous diseases and their etiologic agents into the hands of the practicing physician. Each disease is discussed as a separate entity, with a short account of its distribution, pathology, and clinical features and a more prolonged detailing of the laboratory procedures required for its positive identification. The sections on treatment at the end of each chapter are necessarily short, because so little is known that really helps.

The final chapter on contaminants of the culture medium on which the pathologic material must be grown for such long periods is especially useful, because this is a constant source of error to the uninitiated laboratory worker. A short appendix gives methods for the study of specimens, preparation of media, and stains and directions for animal inoculations with suspected material.

The book is profusely illustrated—a necessity in presenting this subject—and the bibliographies with each chapter are adequate. It is highly recommended as a practical help to all those interested in infectious diseases.

Simplified Diabetic Management. By J. T. Beardwood Jr., M.D., and H. T. Kelly, M.D. Price, $3.00. Pp. 194. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C. 2; 2083 Guy St., Montreal, 1954.

Though rather detailed for a simplified text, this book presents much that is admirable in a philosophic approach to diabetes mellitus, but falls short of its title in some of the details of diabetic management.

The points on hygienic care, variation in the diet, and the degree of control are well taken. However, the use of a dietary pattern artificially contrived to a system of A and B units, instead of the more flexible American Diabetes Association plan which is available and has been accepted throughout the country, certainly is open to criticism. The diet prescription for the adolescent diabetic is somewhat distorted in proportions. In addition, the use of the 7/8 in. needle instead of the standard 5/8 or 1/2 in. needle, plus injection "almost parallel to the surface" is not advisable. Recent papers indicate that the perpendicular type of injection is associated with a lower incidence of local complications. The multiple injections advised if the patient is on more than 15 units of insulin is not a universally accepted technique. Recent screening studies have shown that far more o fthe patients showing glycosuria than the 5% to 6% mentioned in the text prove not to have diabetes when they are further investigated. Self-treatment of "corns" is also to be deplored.

Aside from the above points and several other oversimplifications common to writing for the laity the book does present the essentials of adequate control, through the proper integration of diet and insulin, that is compatible with the patient's leading an almost normal everyday life.

Kleines Diagnostikon. By Dr. Max Barschneider. Price, not given. Pp. 254. Ferdinand Hirt, Schauenburgerstr. 36, Kiel (24b), 1954.

This little book, sturdily bound, gives in alphabetic order the most important subjective and objective symptoms of illness, as well as the respective results of simple laboratory methods. There is a total array of 183 symptoms.

Here is a short example:

No. 59—Facial nerve paralysis:

1. Peripheral (forehead, eye, mouth involved):
   (*a*) Rheumatism, syphilis, diphtheria; in children frequently poliomyelitis
   (*b*) Diseases of the parotid gland: abscesses, tumors
   (*c*) Diseases of the middle ear and os petrosum
   (*d*) Inflammations and tumors of the base of the brain; for instance, acusticus tumor
   (*e*) Trauma
2. Central (frowning possible): apoplexy, cerebral sclerosis, progressive paralysis.

The arrangement of the book is clear and rather complete, in spite of its conciseness, and it should be helpful to the student and general practitioner.

Entstehung, Erkennung, Beurteilung und Behandlung der Herzschmerzanfälle. By Prof. W. H. Hauss. Price, not given. Pp. 394, with 127 illustrations. Georg Thieme Verlag, Stuttgart, Herdweg 63, 1954.

This book presents an elegant discussion from theoretical as well as the practical viewpoints of a subject which seems to gain more and more importance in our turbulent times.

It also deals in full with the problems of coronary occlusion (myocardial infarction), which is not made clear in its title.

The author looks back on 20 years of experimental and clinical experience. Dr. Hauss' style makes enjoyable reading, and what he has to say is instructive and should prove to be very helpful to any physician. Pictures, tables, and diagrams are of excellent clarity in technical and descriptional respects.

The rare causes of heart pain are discussed, as, for instance, myocarditis, tetany, hypoglycemia, pheochromocytoma, inflammation of the coronary arteries, etc.

Of particular interest is what the author calls "the acute syndrome"; fever, leucocytosis with left shift and eosinopenia, high sedimentation rate, albumin-globulin reversal, hyperglycemia, and elevated NPN. Although most of these may happen in many other acute conditions, they surely make a diagnosis of myocardial infarction easier in the presence of severe angina pectoris pain.

Also, the differentiation between large and small infarctions is helpful in the prognosis and therapy of the case.

Blocking of the carotid sinus (the technique of which is described in detail) in severe collapse and the discriminating use of small doses of strophanthin in patients with signs of heart failure are items which should prove to be interesting for the American reader.

Surgery of the Caecum and Colon. By Stanley Aylett, M.B., B.S. Price, $9.00. Pp. 295, with 142 illustrations. E. & S. Livingstone, 16 and 17 Teviot Place, Edinburgh 1, 1954.

Mr. Aylett's textbook on surgery of the cecum and colon is an exposition of current practice at the Gordon Hospital in London.

Starting with brief sections on the anatomy, physiology, and pathology of the large intestine, he proceeds to a detailed discussion of the symptoms, diagnosis, and management of the various surgical diseases of the colon. The commoner diseases are discussed in great detail, while rarer conditions are given little space. Occasionally, as in discussing hemangiomata, he effectively handles the subject by describing the symptomatology and management of illustrative cases. At other times he dismisses rare lesions, such as carcinoids, with a brief paragraph and reference to authoritative source material. The text is well organized and beautifully printed. There are abundant illustrations, some in color. The bibliography is entirely adequate and up-to-date.

The book's strength lies in is abundant line and wash drawings and in the clarity with which the author defends his preferred methods of treatment. Its weakness, particularly for the American reader, is the use of unfamiliar proprietary names and the understandable use of the British Pharmacopoeia and the British idiom.

Altogether, this monograph will make rewarding reading for student, physician, and surgeon. There is enough factual detail to instruct the beginner and enough controversy to stimulate the master.

Menstruation und innere Medizin. By Friedrich-Horst Schulz and H. Knobloch. Price, approximately $5.00. Pp. 219, with 122 illustrations. Georg Thieme Verlag, Stuttgart, Herdweg 63, 1954.

Without claiming or achieving a complete coverage of their subject, the authors succeed in accumulating a great amount of facts and clinical observations within these 208 pages.

Starting with the anatomy and physiology of the menstrual cycle, they discuss the influence of the adrenarche, menarche, menses, and menopause on physiologic aspects of the female system. This is followed by an enumeration of the effects of the menses on the hemopoietic, cardiovascular, respiratory, endocrine, and metabolic systems; the alimentary tract; the muscles and the skeleton; the neurologic system, the mucosal membranes, and the skin.

The third part of the book deals with the influence of the normal adrenarche, menarche, menses, and menopause on the course of internal medical diseases.

After a brief review of faulty diagnosis caused by menstrual influences, the effects of internal medical diseases on the menses are discussed, the menopause and its relations to illnesses are described, and malignant disease and dysmenorrhea in menopause are briefly mentioned.

The last 20 pages offer a comprehensive chapter about drugs influencing the menstrual cycle and an evaluation of the uses and abuses of the female hormones in internal medicine.

Whereas most of the data given by the authors are primarily of statistical value, some of their own observations, for instance those in regard to the skin, are of definite clinical value.

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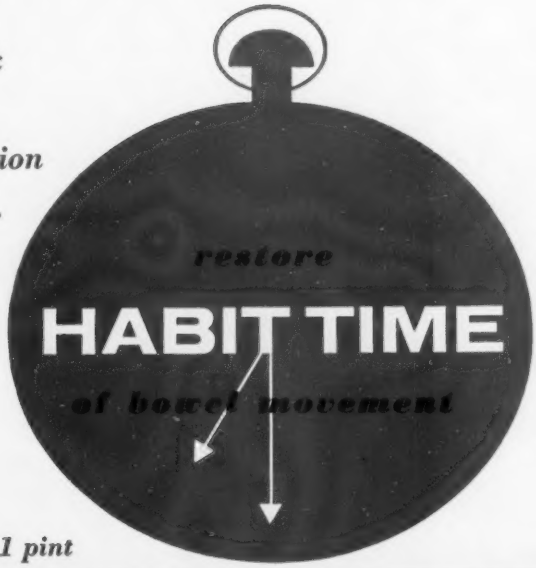

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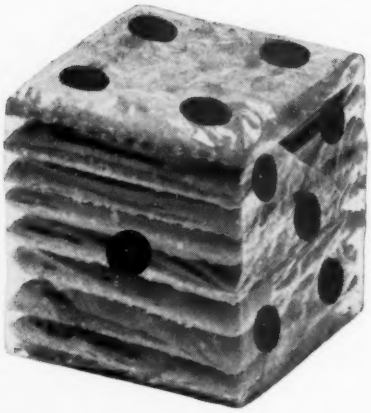

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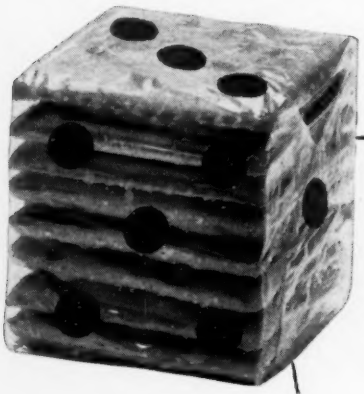

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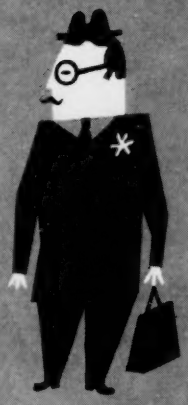

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